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ON THE CLASSIFICATION, NATURAL HISTORY AND TREATMENT OF THE MYOPATHIES

BY

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INTRODUCTION

IN the early part of the nineteenth century numerous reports appeared in the medical literature describing cases in which progressive atrophy of the voluntary muscles occurred. Aran in 1850 gave a detailed clinical description of this syndrome and Wachsmuth (1855) was able to collect a series of 60 reports from the literature. "Granular degeneration of the voluntary muscles" in 4 brothers was described by Meryon in 1852 and it gradually became clear that cases of this type were clinically and pathologically distinct from another group of patients in whom muscular atrophy was secondary to changes in the grey matter of the spinal cord (Luys, 1860) and in whom the disease was not usually familial. However, it was some time before this fact gained general recognition; the pseudo-hypertrophic muscular paralysis of children as described by Duchene (1868) was at first believed to be similar to the progressive muscular atrophy of adult life. The first serious attempt to separate this group of cases from the other forms of muscular atrophy was made by Leyden (1876), who described a familial form of atrophy of muscles of the pelvic girdle and remarked upon the clinical resemblance of his cases to those of pseudo-hypertrophic paralysis. Möbius (1879) went further and included the pseudohypertrophic cases and those of the Leyden type in a separate clinical group. In the meantime, advances in the study of neurological disorders had separated from progressive muscular atrophy a wide variety of other disorders, each showing distinctive clinical and pathological features. Poliomyelitis, polyneuritis, syringomyelia and syphilitic amyotrophy were among the conditions so defined.

It was left to Erb (1884) to extract from the residuum of "progressive

muscular atrophy " those cases in which there was no pathological lesion of the central nervous system and in which the disease appeared to be a primary degeneration of muscles, a muscular dystrophy or myopathy. He pointed out that these cases were clearly distinguishable in symptoms, development and localization of muscle wasting. He described a "juvenile" or scapulohumeral form of the disorder which was quite different from spinal muscular atrophy, and endeavoured to show that the clinical and pathological features in his cases were similar to those in the pseudohypertrophic type of Duchenne (1868) and Gowers (1879) and in the atrophic type of Leyden. These views were soon widely accepted and shortly afterwards a further type of myopathy, in which atrophy began in the face, was defined by Landouzy and Dejerine (1884) and has since been called the facioscapulohumeral form.

Some years later a distal type was added to the group (Gowers, 1902), and Batten (1909–10) endeavoured to show that certain cases of amyotonia congenita (Oppenheim, 1911) were myopathic in nature, a so-called " simple atrophic myopathy." Aldren Turner (1940 and 1949) has confirmed Batten's view and has demonstrated that a small proportion of cases of amyotonia may indeed be due to a benign congenital myopathy. Nevin (1936) endeavoured to define a further clinical group of cases in which a myopathy of late onset (after the age of 30) occurred, while Barnes (1932) described a family, apparently unique, in which hypertrophic, pseudohypertrophic and terminal atrophic stages occurred, the terminal wasting being distal in distribution.

Within recent years it has been recognized that in facioscapulohumeral dystrophy particularly, a certain proportion of affected individuals may show only minimal evidence of the disease with striking lack of progress (Tyler and Stephens, 1950) and this probably explains most of the reported cases of local non-progressive myopathy (Crouzon, Lechelle and Bourguignon, 1930). However, a number of other cases have been described in which the myopathic process has been limited to the quadriceps (Bramwell, 1922–3; Denny-Brown, 1939) and it seems probable that this syndrome is a distinct clinical entity; rarely, similar changes may occur in other muscles such as the gastrocnemius and soleus (Weaver and Maun, 1942). A myopathic process limited to the external ocular muscles is also well recognized; a case of this type was described by Hutchinson in 1879 and Fuchs (1890) showed that the pathological changes were primary in the muscles. Although the disease is often limited to the ocular muscles it must be pointed out that in a proportion of such cases the myopathy may extend to muscles of the limbs and trunk (Kiloh and Nevin, 1951).

An important group of cases not yet referred to are those of myotonia

congenita and dystrophia myotonica. The first detailed description of myotonia congenita was that of Thomsen (1876) who described the condition as it affected himself and other members of his family. Strictly speaking, if this condition is a separate entity, it cannot be described as a myopathy, as the patient's disability is entirely due to the phenomenon of myotonia (failure of muscular relaxation after contraction) and there is no muscular degeneration. The same must be said of paramyotonia (Eulenburg, 1886) in which myotonia only occurs on exposure to cold. In the much commoner dystrophia myotonica, however, which was described by Batten and Gibb (1909) and by Steinert (1909), a distal myopathy, cataract, mental and endocrine changes are seen, as well as myotonia. Many authors continue to believe that myotonia congenita, paramyotonia and dystrophia myotonica are separate clinical entities, but Maas and Paterson (1939, 1950) and others are of the opinion that all three syndromes are variations of a single disease process.

In addition to the clinical groups referred to above, in which the disease appears to be of genetic origin, a number of cases of atypical myopathy associated with specific defects of metabolism have been described (McArdle, 1951: Acheson and McAlpine, 1953) and it is also well known that a myopathy may complicate thyrotoxicosis. A form of " menopausal muscular dystrophy " responding to treatment with cortisone or wheat germ has also been described (Shy and McEachern, 1951) but it must be pointed out that the pathological changes in the muscles in such cases are different from those observed in cases of classical myopathy. The same may well have been true of the small group of cases of myopathy in childhood in which recovery occurred, either spontaneously or after treatment with wheat germ derivatives (Walton and Nattrass, 1954). An increasing volume of clinico-pathological evidence suggests that cases of this type are in reality examples of polymyositis and not of muscular dystrophy. It is also true to say that other cases of myopathy are seen from time to time which cannot adequately be classified according to the published reports referred to above. In this small group of atypical and transitional cases (Batten 1909–10) it is perhaps possible to define one other very rare clinical syndrome in which a myopathy is combined with the type of muscular fatigability seen in myasthenia gravis. Laurent (1951) has observed at least one case in which myopathic wasting and weakness responded to treatment with prostigmine and the authors have observed a similar case, in which fatigability occurred, again responding to prostigmine and inviting a diagnosis of " myasthenic myopathy."

During the twentieth century a great deal has been written concerning the clinical features, mode of inheritance, pathogenesis and treatment of

the various myopathies, and it is now well recognized that the great majority of cases are genetic in origin, though the exact pathogenesis of the muscular wasting remains a mystery. While much has been learned, it is true to say that the mode of inheritance of the various forms is not fully understood. This fact can be largely attributed to the lack of any general agreement concerning the classification of the myopathies and to the confusion resulting from the attempts made by some authors to consider the inheritance of all forms of muscular dystrophy together. There is also wide disagreement as to the value of treatment, since enthusiastic claims of the therapeutic value of numerous remedies, particularly vitamin E, have been made in recent years, but many other workers have failed to reproduce the results achieved.

In this paper a new classification of the myopathies is proposed, based upon a review of the clinical features and natural history of the disease in 105 cases of myopathy of various types. The results of a controlled trial of several forms of treatment in these cases will also be described. The cases to be reviewed will be enumerated and the methods of the investigation detailed when the proposed classification has been considered.

Classification

Consideration of the historical notes given in the introduction reveals that the following types of myopathic disorder have been described:

(1) Pseudohypertrophic muscular dystrophy (Duchenne; Gowers).
(2) The pelvic girdle atrophic type (Leyden-Möbius).
(3) The juvenile (scapulohumeral) type (Erb).
(4) The facioscapulohumeral type (Landouzy-Dejerine).
(5) The distal type (Gowers).
(6) The late juvenile type (Nevin).
(7) The Barnes type.
(8) Myotonia congenita (Thomsen) and paramyotonia congenita (Eulenburg).
(9) Dystrophia myotonica (Steinert; Batten and Gibb).
(10) The simple atrophic type of amyotonia congenita (Batten)—the congenital myopathy of Aldren Turner.
(11) The local myopathies (Bramwell; Denny-Brown; Weaver and Maun).
(12) Ocular myopathy (Hutchinson; Fuchs; Kiloh and Nevin).
(13) Menopausal muscular dystrophy (Shy and McEachern).
(14) Benign childhood myopathy (probably polymyositis) (Walton and Nattrass).

(15) Unusual myopathies of metabolic origin (McArdle; Acheson and McAlpine).
(16) Thyrotoxic myopathy.
(17) " Myasthenic myopathy."
(18) Atypical myopathy.

The above list is an attempt to enumerate all the forms of myopathy previously described, but it is clearly much too unwieldy for routine use. It includes many conditions which are of extreme rarity and it is quite possible that the distinctions between other groups are artificial. So long as the existence of the rarer forms of myopathy is recognized, they can be discarded from further consideration in any attempt to define the broad groups into which the majority of cases can be classified. We can therefore leave aside the atypical and " myasthenic " cases, the benign childhood type, the myopathies of metabolic and endocrine origin and the cases with localized muscular change. The menopausal cases are probably unrelated to the classical myopathies, particularly in view of the pathological findings, and may similarly be excluded.

We are therefore left, on the one hand, with the traditional types of muscular dystrophy (pseudohypertrophic, atrophic pelvifemoral, juvenile scapulohumeral, late juvenile, facioscapulohumeral and distal) to which may be added the Barnes, ocular and benign congenital types, and, on the other, myotonia congenita, paramyotonia and dystrophia myotonica. A division into these two main groups, one containing the pure muscular dystrophies, the other all myotonic cases, seems justifiable clinically and this distinction is certainly made by the great majority of authors. It must, however, be pointed out that despite the myotonia and the ocular and endocrine changes which so clearly distinguish dystrophia myotonica from the other myopathies, the pathological changes in the wasted muscles are very similar in the two groups of disorders. Furthermore, myopathic affection of the ocular muscles may occur in both, while the clinical manifestations in the family described by Barnes showed certain resemblances to the distal form of myopathy on the one hand and to dystrophia myotonica on the other. However, despite these grounds for comparison of the two groups, it must be agreed that the available evidence clearly indicates that they are distinct both clinically and genetically and they will be considered as such in this paper.

The classification of the muscular dystrophies.—In considering the classifications which have been proposed for this group, it is possible first to dismiss briefly the relatively uncommon groups such as that of Barnes and the congenital and ocular types. The resemblance of the findings in

Barnes' cases to those in the distal myopathy of Gowers and in dystrophia myotonica has already been mentioned. The comparison with the myotonic cases is particularly apt when one considers the dominant mode of inheritance and the fact that the early stage of muscular hypertrophy is very like that sometimes seen in myotonia congenita, while the late stage of distal wasting resembles the limb changes in advanced dystrophia myotonica. This concept would certainly be compatible with the view of Maas and Paterson (1939, 1950) that myotonia congenita is an early stage of dystrophia myotonica, but the absence of myotonia (save in one case) and of cataract and endocrine abnormalities in Barnes' cases would make it presumptuous to assume that his family was one of dystrophia myotonica. It is probably preferable to suggest that he described a unique form of myopathy, of dominant inheritance, which has not been observed by other workers.

The familial congenital myopathy or myopathic form of amyotonia congenita as described by Aldren Turner (1940 and 1949) must also be considered as a distinct clinical entity. This assumption seems justifiable despite the fact that in the only other comparable case described in the literature, in which a child who had had amyotonia congenita was shown to be suffering from a myopathy in adolescence (Silvestri, 1909), there was a history of facioscapulohumeral dystrophy in a maternal aunt. Two cases which may fall into this group have been described recently by the authors (Walton and Nattrass, 1954; Cases 7 and 8). Despite the single observation of a family history of myopathy in Silvestri's case, the clinical features in this small group of cases are so distinctive that it would seem justifiable for the present to regard them as a separate group.

The same would seem to be true, in the present state of knowledge, of the ocular cases. Kiloh and Nevin (1951) point out, in their exhaustive review, that involvement of the ocular muscles in the classical types of myopathy is extremely rare, although it has been described in at least 2 cases showing a clinical resemblance to facioscapulohumeral dystrophy (Winkler and Van der Weyde, 1889; Von Seeligmüller, 1889). However, these patients did not have relatives with myopathy and it is true to say that none of the recent extensive reports of families with facioscapulohumeral myopathy mention ocular involvement as a significant feature of the disease even though Landouzy and Dejerine described a case with ocular palsy. In the large number of cases reviewed by Kiloh and Nevin, and in their 5 personal cases, the disease seemed to begin in the extrinsic ocular muscles and was sometimes limited to them, although a considerable proportion of the patients had weakness of the facial musculature (particularly orbicularis oculi) and in others the muscles of the shoulder girdle

were involved. Pelvic girdle muscles were rarely affected and it was not often that the patients made any spontaneous complaint of limb weakness; often changes other than in the eyes were only discovered on careful physical examination. About half of the cases reviewed, including all 5 of their own, were isolated, but in the remainder other members of the family were involved. However, from the information given, no clear pattern of inheritance emerges and it is clear that much work remains to be done before the mode or modes of transmission of this type of myopathy can be defined. Kiloh and Nevin remarked that ocular myopathy appears to approach most closely in its general characteristics to the Landouzy-Dejerine type, but in view of the resemblance of the pathological changes to those observed in other forms of myopathy they did not propose to separate these cases as a rigid group. While it is agreed that too rigid a classification is probably unwise in view of the constant histological changes observed in all forms of myopathy, it is clear that several of the forms differ in their clinical and genetic characteristics and in view of the distinctive features of ocular myopathy it is believed that these cases should be classified separately.

The great majority of the commonly occurring cases of myopathy can be classified, using traditional criteria, into one of the remaining groups (pseudohypertrophic—Duchenne, atrophic pelvifemoral—Leyden-Möbius, juvenile sacpulohumeral—Erb, facioscapulohumeral—Landouzy-Dejerine, late juvenile—Nevin, distal—Gowers). Many authors, in reviewing large series of cases, have accepted these main groups in classifying their patients (Hurwitz, 1936; Sjövall, 1936); some, notably Milhorat and Wolff (1943*a*) have endeavoured to consider all forms of muscular dystrophy as one clinical entity, while others (Bell, 1943; Tyler and Wintrobe, 1950; Levison, 1951; Stevenson, 1953) have concluded that many of the distinctions made between the groups are artificial, and have attempted to produce a simplified classification on the basis of clinical and genetic criteria. The various simplifications proposed by the latter authors have each much to commend them and will be considered in more detail shortly; however, the classification, or lack of classification, attempted by Milhorat and Wolff and by the authors of many of the papers they reviewed is to be deplored as being likely to obscure both the patterns of inheritance and the distinctive clinical pictures of the various types of myopathy.

The two groups of cases which have been most commonly looked upon as being artificially defined are the late juvenile cases (Nevin) and the distal ones (Gowers). In fact, the two cases described in Nevin's original paper in 1936 may not have been cases of classical myopathy, since the histological changes in the muscles were unusual, closely resembling those

observed by Shy and McEachern (1951) in patients with "menopausal muscular dystrophy." Nevin also referred briefly to a case of Dr. Critchley's in whom myopathic weakness of the shoulder girdles had begun at the age of 46, but the patient also had weakness of eye closure and was probably a case of facioscapulohumeral myopathy. However, he also reviewed 16 reported cases, in all of which the clinical findings were typical of Erb's juvenile myopathy save for the age of onset, which was invariably over the age of 30 years. It now seems likely that a distinction purely on the ground of age is an artificial one, and there appears to be no reason why, in view of the identical clinical picture, these cases should not be included with the juvenile myopathies beginning at an earlier age. Nevin also discussed 6 reported cases of distal myopathy of late onset: he pointed out that in several of these patients proximal muscles were also involved and he saw no reason why they should be separated from the late juvenile cases. Numerous authors (e.g. Critchley, 1949) have questioned the existence of a distinctive distal form of myopathy despite several clear clinical descriptions in the literature (e.g. Milhorat and Wolff, 1943*b*) while Bell (1943), Tyler and Wintrobe (1950) and Stevenson (1953) have not considered this type in formulating their classifications of myopathy; Stevenson recognized that a distal form did occur but felt that it was readily distinguishable clinically from "muscular dystrophy in the more usual sense of the term." However, the work of Welander (1950 and 1951) has shown conclusively that such a clinical type does occur and that it may breed true as a Mendelian dominant factor. There can be little doubt that this form of myopathy does exist, and that it is clinically and genetically distinctive.

Bell (1943), in an exhaustive survey of the literature, reviewed 1,228 published cases of myopathy and another 113 gleaned from the records of the National Hospital, Queen Square; she made a determined effort at classification based on information derived from these cases. She classified them firstly on the basis of clinical criteria—dividing them into three groups. These were:

A. Pseudohypertrophic: this group included all cases with pseudohypertrophy of muscle but without facial involvement; in these patients the disease usually began in the lower limbs.

B. Atrophic: these cases did not show pseudohypertrophy or affection of the face, and weakness and wasting usually began in the shoulder girdles and upper limbs.

C. All cases with facial involvement: occasional cases in this group showed pseudohypertrophy of muscles.

In general, the age of onset was early and the progress of the disease

comparatively rapid in Group A cases while the onset was later and the disease progressed very slowly in those of Group C, so that a considerable proportion of individuals in the latter group lived to a normal age. Group B cases were on the whole intermediate between those of Groups A and C in both respects. Bell remarked, from her study of numerous pedigrees, that it was also possible to distinguish three genetic groups (sex-linked recessive, autosomal dominant and autosomal recessive). There was a considerable degree of correspondence between the clinical and genetic groups, a sex-linked recessive form of inheritance being most common in the Group A cases, an autosomal recessive in Group B and an autosomal dominant in Group C, but this correlation was by no means complete, since examples of all three modes of inheritance were found in each of the clinical groups. It was probably this fact which led to her remark that there was a considerable overlap between the three clinical groups and to her assumption that the same main gene could produce any of the three types, even though she admitted that the condition usually bred true in individual families, particularly those of the Duchenne type. This classification of Bell's and the conclusions based upon it have been widely criticized, particularly by Tyler and Wintrobe (1950) and by Stevenson (1953).

Tyler and Wintrobe condemn particularly "her rather uncritical attempt to include all cases described in the literature as dystrophy," pointing out that many relatives of the patients in the families she reviewed had not been examined, so that it was impossible to be sure that they were not affected. They believe that her approach led to an unnecessarily complex classification. Similar criticisms have been offered by Stevenson who has also pointed out that the single clinical sign of pseudohypertrophy is an unsatisfactory criterion of classification. Dependence upon this feature would mean that the occasional cases of the Erb type showing this phenomenon would be included in Bell's Group A, while cases of the Duchenne type without this sign would be classified in Group B. He also remarked, in discussing those few of Bell's Group C cases in which the disease appeared to be transmitted as a sex-linked recessive, that the evidence of facial involvement was slight.

The classification proposed by Tyler and Wintrobe (1950) has the great advantage of simplicity. They suggest that all cases of dystrophy can be classified into two groups, the childhood group and the facioscapulohumeral. The childhood type begins in early childhood, occurs mainly in males, is frequently inherited as a sex-linked recessive trait, involves the axial and pelvic musculature, almost completely spares the facial muscles, is often accompanied by muscular enlargement, is rapidly progressive and seldom compatible with survival to adult life. According to

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their criteria, this group includes the pseudohypertrophic (Duchenne) cases and the atrophic pelvifemoral cases (Leyden-Möbius) occurring in childhood. The facioscapulohumeral type, on the other hand, usually begins in late childhood or adolescence, is transmitted as a Mendelian dominant affecting both sexes equally, involves the face and pectoral muscles and is rarely accompanied by pseudohypertrophy; the disease is slowly progressive and only a small percentage of afflicted individuals are incapacitated before old age. The authors suggest that this group contains the classical Landouzy-Dejerine type of myopathy and Erb's juvenile type. They remarked that, from their observation of 175 cases of myopathy, cases had remained true to this classification within an individual family. They had only observed 3 patients who did not satisfy their criteria; 2 were girls in the third decade, whose disease had begun in childhood with pseudohypertrophy and rapid progression, and the third was a similar condition in a man of 56. Undoubtedly the groupings proposed by Tyler and Wintrobe are simple and explain satisfactorily the cases which they observed. It must, however, be pointed out that the great majority, if not all, of their patients with facioscapulohumeral dystrophy were members of a single family, and they do not seem to have observed any cases of the juvenile or Erb type of dystrophy which are well known to other workers. In view of the complete absence of facial involvement in these latter cases, which only rarely show a dominant mode of inheritance, many authors have preferred to consider them as a distinct group, rather than to classify them with the clearly defined facioscapulohumeral cases.

Levison (1951), in a review of cases observed in Denmark, attempted to classify them in the traditional manner, but found that he could not distinguish the Duchenne and Leyden-Möbius types. He therefore divided his patients into three clinical groups, the first consisting of the Duchenne and Leyden-Möbius types, the second containing the scapulohumeral type and the third the facioscapulohumeral. In his first group there were examples of sex-linked recessive, autosomal recessive and autosomal dominant inheritance, while in the other two groups only the two autosomal mechanisms appeared to be involved: dominant inheritance was almost invariable in the facioscapulohumeral cases. The confused pattern of inheritance in Levison's first group seems most likely to have been due to incorrect classification of some of his cases, particularly those of the traditional Leyden-Möbius type. While it is true that many childhood cases in the atrophic pelvifemoral group of Leyden-Möbius are clinically indistinguishable from cases of the Duchenne type, save for the absence of pseudohypertrophy, others, often beginning at a later age, are entirely different in their clinical features and rate of progress, corresponding in

this respect to the juvenile scapulohumeral cases and differing only in the fact that weakness begins in the pelvic girdle musculature and not in the upper limbs. It seems probable that if these latter patients were transferred to Levison's second group, his first (containing cases of the Duchenne type and the childhood Leyden-Möbius cases with a similar natural history) would then correspond to Tyler and Wintrobe's childhood group, showing almost invariably a sex-linked recessive mode of inheritance.

The most recent attempt at classification has been made by Stevenson (1953), in a review of 51 families of myopathy observed in Northern Ireland. He commends the concept of " childhood muscular dystrophy " as described by Tyler and Wintrobe but objects to certain of the reservations given in their definition. In particular, he feels that clear definition of this group is invalidated by the remarks that the condition " nearly always affects males " and " almost completely spares the facial muscles." He agrees that in such a classification these reservations are necessary in view of the occasional onset in childhood of facioscapulohumeral myopathy and of other forms of slowly progressive myopathy which occur in both sexes in certain families. He examines in detail all the reported cases in which the Duchenne type of pseudohypertrophic muscular dystrophy had been reported to occur in girls and points out that not one of them appeared to be typical. Although from time to time a very similar *initial* clinical picture in a girl had been described, in all cases the condition progressed much more slowly, allowing the individual to reach adult life. This point was clearly of the utmost importance in deciding whether the classical Duchenne form of myopathy was invariably transmitted through a sex-linked recessive gene. In view of the failure of affected boys to reproduce, it would be expected that affected females would occur even less frequently than in hæmophilia. On the other hand, if the condition were not always inherited in this manner, it would be expected that occasional affected brothers and sisters would occur, but no undoubted family of such a type had ever been reported. After reviewing his own cases, Stevenson concluded that the " Duchenne type rapidly progressive muscular dystrophy of young boys " was a separate, clearly defined entity, which was invariably transmitted via a sex-linked recessive gene, with a high rate of mutation.

With regard to the remaining cases, Stevenson remarked that from Bell's analysis it was clear that any of the other forms of dystrophy could be inherited by a dominant or a recessive mechanism. In the non-Duchenne type cases reviewed by Bell, the inheritance was dominant in roughly half and recessive in the remainder. Whereas in Denmark (Levison, 1951) and in Utah (Tyler and Stephens, 1950) facioscapulohumeral dystrophy was inherited as a dominant trait, in other reported families and in

Northern Ireland the inheritance was as a recessive. He also felt that the clinical course of the disease in the cases without facial involvement and with primary affection of either the pelvic or shoulder girdles was broadly similar to that in the facioscapulohumeral group. He therefore concluded that any distinction between these cases would be an artificial one, and suggested that they should be termed "autosomal limb-girdle muscular dystrophy"; all cases falling into this group were probably variable expressions of a common genotype.

The final classification reached by Stevenson therefore consisted of two groups; the first, the Duchenne type rapidly progressive muscular dystrophy of young boys, is characterized by (*a*) expression solely in the male, (*b*) onset mainly in the first two years of life, (*c*) high frequency of pseudohypertrophy of calves, (*d*) universal affection of gluteal, thigh adductors and later scapulohumeral muscles, (*e*) rapid progression to inability to walk usually before the age of 12 and death in the teens, and (*f*) inheritance via a sex-linked recessive gene with a relatively high mutation rate. The second group, autosomal limb-girdle muscular dystrophy, contains a large number of cases varying in age of onset, clinical signs and symptoms; in some the condition begins in the pelvic girdle, in others in the shoulder girdle, and in yet others the face is affected, but within a sibship where more than one member is affected these factors vary remarkably little; it is concluded that there are sound reasons for supposing that in all these cases the condition is determined by the same gene mutation or by slight variations or varying expressions thereof.

It must be agreed that any attempt to simplify the complex terminology and classification of muscular dystrophy is worth while and for this reason the efforts of Tyler and Wintrobe and of Stevenson to do so are particularly commendable. The criticism levelled at Bell's classification by each of these workers seems well justified. Her survey was monumental in design and execution, but inevitably suffered from the failing which threatens any such review of published cases; inaccuracies and misconceptions in only a few of the reports considered would inevitably lead to distortion of the final schema. It was probably these failings, combined with her acceptance of the single feature of pseudohypertrophy as a criterion for inclusion in her Group A, which led to the undue complexity of her classification, both from the clinical and the genetic standpoint. On the other hand, it is our view that both the Utah workers and Stevenson have approached the opposite extreme by attempting an over-simplification, which may have been indicated by the clinical material they observed but does not fully explain the facts as seen by other competent observers.

We have already given reasons for suggesting that distal myopathy,

congenital myopathy and the ocular and Barnes types must be considered for the present as uncommon but clinically and genetically distinctive groups. Nor do we feel, on the basis of our observations of a large series of cases, that it is justifiable to divide the remainder of the dystrophies into only two groups, either " childhood " and " facioscapulohumeral " as proposed by Tyler and Wintrobe, or " Duchenne type rapidly progressive muscular dystrophy of young boys " and " autosomal limb-girdle muscular dystrophy " as suggested by Stevenson. The classification of Tyler and Wintrobe is particularly vulnerable: Stevenson's reasons for rejecting the term " childhood " muscular dystrophy seem valid, while it is surely unsatisfactory to use " facioscapulohumeral " as a title for a group of patients when a considerable proportion of them do not show facial involvement. Stevenson's divisions also seem unsatisfactory since our observations suggest that his Duchenne group is defined too rigidly, while his autosomal limb-girdle group is loosely drawn, including at least two conditions which seem to us clinically and genetically distinct.

In order to substantiate our criticisms and to formulate what seems to us a more satisfactory classification it will now be necessary to anticipate some of the clinical observations which are to be described at a later stage in this paper and also certain details of inheritance which will be given in a subsequent communication on the genetics of the complaint. We believe that it is of considerable importance to define the groups into which patients with myopathy can be classified, not only for academic interest, but also because of the wide variations observed in the natural history and inheritance of the various types. Accurate diagnosis is thus important from both the prognostic and the eugenic standpoints. In dividing our cases we have endeavoured to avoid the pitfalls of classifying cases according to a single criterion, such as muscular hypertrophy, but in each instance we have taken into account the clinical picture of the disease, including the pattern of muscle involvement and the natural history, together with the mode of inheritance suggested by our studies of families. As a foundation upon which to build we shall take Stevenson's classification and shall endeavour to show how our observations agree or disagree with his criteria.

To take first his " Duchenne type rapidly progressive muscular dystrophy of young boys "; we agree that this title is more satisfactory than " pseudohypertrophic muscular dystrophy " in view of the occasional occurrence of muscular enlargement in the other forms of myopathy. We must accept this valid criticism while recognizing that pseudohypertrophy is infinitely more common in this form of the disease than in any other. We are also agreed that all the available evidence points to a sex-linked

recessive form of inheritance in this group of cases. Our personal observation of 48 cases and our knowledge of 57 cases in 39 sibships of 34 families gives ample support for this view, although it is evident that many cases must be accounted for by mutation. However, we are confident that Stevenson's criteria for including cases within this group, and particularly the suffix "of young boys," are much too rigid in view of the observed facts. While it is true that a very large proportion of patients within this group are unable to walk by the age of 12 years, and die in the teens, it is also clear that in occasional cases the age of onset may be later and the progression of the disease slower, even though it is still possible from all clinical and genetic evidence to classify them as "Duchenne type rapidly progressive muscular dystrophy"—rapidly progressive, that is, in comparison with the other forms of myopathy. In support of this opinion we append the pedigrees (figs. 1 to 3) of three families in which the clinical picture in the affected individuals was typical of the Duchenne type save for the age of onset and rate of progression. It will readily be seen that the pattern of inheritance in all 3 families is characteristic of that due to a sex-linked recessive gene. In family D.6 (fig. 1), the disease in II,3 began at the age of 18 years; he was unable to walk when he was 26 and died at the age of 31. Difficulty in walking in II,9 was first experienced at the age of 26, he was confined to a wheel-chair when aged 30, and now, at the age of 44, he is grossly deformed and almost completely immobile, and has been bedridden in an institution for ten years. In III,1, III,3, III,5 and III,6 the disease began at 11, 14, 10 and 9 years respectively; III,1 became unable to walk at the age of 20 and is now almost bedridden at the age of 26;

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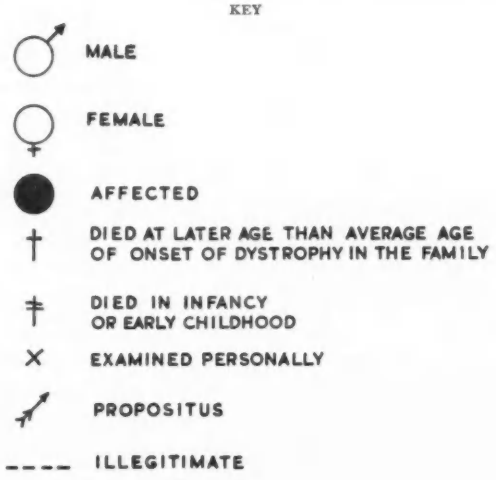

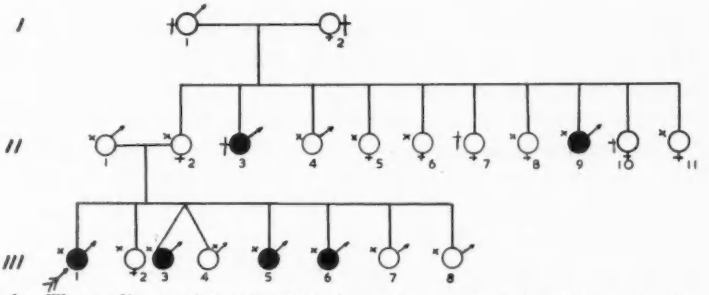

FIG. 1.—The pedigree of family D.6. A key is appended (p. 182) to explain the meaning of the symbols.

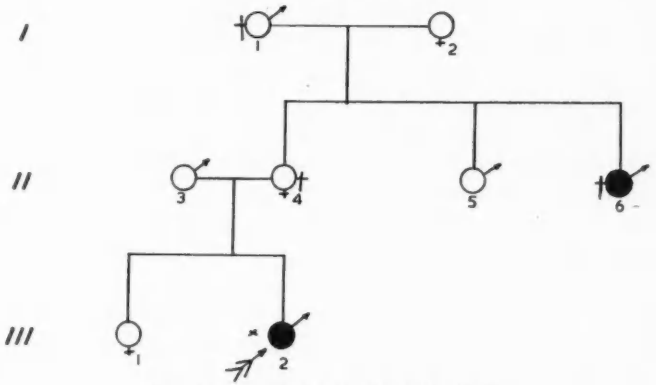

FIG. 2.—The pedigree of family D.9.

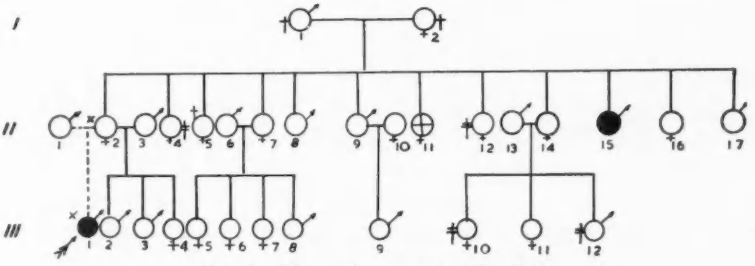

FIG. 3.—The pedigree of family D.19.

the other 3 patients are all able to walk, though with difficulty, at the respective ages of 23, 20 and 12 years. In case II,4 of family D.9 (fig. 2) the first symptoms of muscular weakness were noted at the age of 7 years; he became unable to walk at the age of 17 but did not die until he was 49 years old. Similarly, the onset in III,2 was at the age of 6 years; when last seen, at the age of 17, he was just able to walk. In family D.19 (fig. 3),

II,15 was first affected at the age of 7 years and can still walk at the age of 22 years, while III,1 is walking, though with some difficulty, at the age of 21 years, his disease having begun when he was 8. It is worth noting that in these three families the general pattern of onset and progress was fairly comparable in all the affected individuals; despite the distinct variation from the usual mode of expression of the gene, the condition appeared to "breed true," so far as age of onset and clinical course was concerned, in each of them. In view of this evidence, we have included in this group another 5 male patients in whom the disease began later and progressed more slowly than in the typical case of early onset, although in each instance the clinical picture (including marked muscular pseudohypertrophy) was otherwise indistinguishable and the disease was nevertheless more rapidly disabling than in any other form of myopathy. One of these patients married at the age of 19 and has 4 children though he is now severely disabled at the age of 28. Undoubtedly, according to Stevenson's criteria, these 5 cases, and those in the families described above, would have been classified in his autosomal limb-girdle group, despite the evidence for sex-linked recessive inheritance.

It remains to consider the possible occurrence of this form of the disease in females. Stevenson has rejected all the cases in which this has been said to have occurred, pointing out that in most instances the affected girls were still active in adult life. He does, however, refer to a case of Sjövall's (1936), a girl whose disease began at the age of 3 and who was helpless at 21; this rate of progression of the disease is not very different from that observed in Stevenson's boys. His reason for rejecting these cases is because their acceptance might invalidate the concept of invariable sex-linked recessive inheritance. Our patient who had children is probably unique and in view of the rarity of this event one would not expect affected females to occur with any degree of frequency. However it is clear that this gene is one with a high mutation rate and there is no reason why such a mutation should not occur on the X-chromosome of a male subject as well as in the female. This would not cause the gene to manifest itself in his female offspring unless he were to mate with a carrier female or with one in whom a similar mutation had occurred. It is admitted that if this course of events came to pass, the disease would be expected to occur in male and female members of a single sibship, an event which does not appear to have been reported. Despite this qualification, the mechanism described could certainly account for very occasional cases in females without invalidating the concept of invariable sex-linked recessive inheritance. A comparison with hæmophilia springs to mind; it is now believed that certain isolated cases of bleeding disease in females may be examples

of true hæmophilia (Biggs and Macfarlane, 1953). Leaving speculation aside, we are inclined to admit that, from the point of view of physical findings and natural history at least, the Duchenne type of dystrophy does occasionally occur in girls. From the point of view of prognosis we feel that it is important to recognize this fact; 3 of our 48 personal cases were girls in whom the clinical picture and rate of progress were similar to those in male patients of the same age. 2 of these girls had no siblings, the other had a younger brother and sister, both apparently unaffected; there were no cases of myopathy in earlier generations. The patients were aged 11, 10 and 5 years when first seen; the disease had begun at 4, 6 and 1 years respectively and in all of them had shown comparatively rapid progress, though it is true to say that none of them was so severely disabled as some of the boys of comparable age. It may be that when this type of the disease does occur in girls, it progresses rather more slowly than in the average male case: nevertheless the condition is never so insidious as in the limb-girdle cases to be discussed shortly. We can see no advantage in separating these patients from others in the Duchenne group, particularly since we have shown that the disease in this type of case does not invariably progress as quickly as Stevenson has suggested. We are therefore led to define our first group of cases as one in which the disease (*a*) generally affects males but rarely females, (*b*) usually begins in the first year or two of life but occasionally much later, (*c*) is transmitted as a sex-linked recessive character, and (*d*) usually progresses rapidly, giving total disablement and often death in adolescence, but is sometimes compatible with survival to adult life. Clinical criteria may be added to this list when we have reviewed the findings in our cases. Undoubtedly this group, as defined by us, is much less compact than Stevenson's but we believe that a rigid classification such as he proposed is not justified by the facts. In our opinion the group should be entitled simply "*Duchenne type muscular dystrophy*." This group will include the traditional "pseudohypertrophic muscular dystrophy," though it must be stressed again that it will not embrace all patients showing the phenomenon of pseudohypertrophy, nor is the latter sign a condition of inclusion, since many of the artificially defined "atrophic pelvifemoral" cases of Leyden and Möbius, beginning in childhood, will also be included.

Stevenson's second group of "autosomal limb-girdle muscular dystrophy" is a large one, very variable in its manifestations and mode of inheritance; in 9 of his families in this group the facial muscles were involved, in 14 they were not. Apart from this single feature of facial involvement Stevenson did not feel that there were any other distinguishing characteristics sufficient to divide these patients into two groups. Fur-

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thermore, in his cases, the pattern of inheritance pointed to an autosomal recessive gene both in the families with affected faces and in those without this sign. These features led Stevenson to conclude that in all 23 families the condition was determined by the same gene mutation or by slight variations or varying expressions thereof. It must be admitted that, taking into account the findings in Stevenson's own cases, his conclusions seem well justified. On the other hand, it is doubtful whether his families were a truly representative group, since many other workers have shown that in facioscapulohumeral myopathy the disease is usually transmitted as a dominant factor (Bell, 1943; Boyes, Fraser, Lawler and Mackenzie, 1949; Tyler and Stephens, 1950; Levison, 1951), while in scapulohumeral cases without facial involvement, an autosomal recessive gene can usually be implicated (Bell). Furthermore, there is some evidence to show that the age of onset may be significantly lower and the duration of the disease shorter in cases without facial involvement (Bell) and indeed it seems probable that the natural history of the disease is different, being more benign when the face is involved. It is also true to say that abortive or stationary cases are commonly observed in families with facioscapulohumeral myopathy; it is doubtful whether this phenomenon is ever seen in the true scapulohumeral cases, although it must be admitted that in such an abortive case, facial involvement is often minimal. This question of minor facial involvement is of the greatest importance and may well be one reason for confusion in published work, since many cases which were truly facioscapulohumeral may have been classified as scapulohumeral. It often requires considerable neurological experience to decide whether a particular individual in a facioscapulohumeral family is affected or not and it is certainly valueless to accept a patient's account of the condition of his relatives, since many individuals are unaware of the fact that they have any muscular disorder. This fact is probably the explanation of certain reports of alleged recessive inheritance in families of facioscapulohumeral myopathy; careful examination of apparently unaffected relatives might have brought to light examples of minor degrees of the disease, indicating a dominant form of inheritance. Stevenson's families with recessive inheritance can be exempted from this suggestion since it is clear that he examined the relatives whenever possible, but it seems to us from our experience and from the evidence produced by other workers that his experience was unusual.

As a result of our survey, we are confident that it is justifiable, both from the clinical and genetic standpoints, to recognize cases with facial involvement as a separate entity. We have information concerning 22 cases of this type (18 observed personally), of which 15 were fully developed

and 7 abortive, occurring in 13 sibships of 4 families. In all 4 families there was clear evidence of autosomal dominant inheritance, although it seems possible that there was incomplete penetrance in one family and sex limitation in another. Although there was some variation in the rate of progress of the disease in individual cases, it is true to say that the condition was essentially benign in the great majority, allowing survival and considerable mobility for very many years. We believe that this group of cases should continue to be called by the traditional name of *facioscapulohumeral muscular dystrophy*. The condition is characterized by (*a*) variable age of onset at any time from early childhood until adult life, (*b*) involvement of facial and scapulohumeral muscles and sometimes the pelvic girdle, (*c*) transmission usually by an autosomal dominant gene, rarely by an autosomal recessive, (*d*) the occurrence of abortive cases, (*e*) an essentially benign course, often compatible with survival to a normal age. It may be possible later to add other clinical criteria for inclusion in this definition.

We are now left to consider the cases without facial involvement which would also be classified by Stevenson in his " autosomal limb-girdle " group. We have obtained information concerning 21 such patients (18 personally observed), occurring in 19 sibships of 18 families. According to the traditional groupings 13 of these cases would have been classified as scapulohumeral (Erb), since the muscular weakness began in the shoulder girdles, 5 as atrophic pelvifemoral (Leyden-Möbius), as the pelvic girdle and thigh muscles were first affected, and 3 as late juvenile (Nevin), as symptoms of the disease first appeared after the age of 40 years. Our observations have not indicated any significant differences in the natural history or mode of inheritance in these cases which could be related to the pattern of muscular affection or the age of onset. On the other hand, the group as a whole has seemed to us to show certain significant variations from the features we noted in the facioscapulohumeral group. Although the age of onset varied widely over a range even greater than that seen in cases of the latter type, the disease generally progressed more quickly, often producing considerable disability at an earlier age; even so, the condition was invariably more benign than the Duchenne type. No truly abortive cases of this type were seen and, except in one family, the pattern of inheritance was suggestive of transmission via an autosomal recessive gene. Indeed, 16 of the cases were isolated, some occurring in large sibships; 1 female patient had 1 affected and 2 unaffected brothers, while in the only atypical family, the propositus said that his mother and brother had both suffered from the disease, but both were dead and no medical records were available. This was the only family in which there was any suggestion

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of a dominant form of inheritance, there being no consanguinity. However, in the absence of clinical confirmation, this impression cannot be confirmed. In our opinion, these cases should be regarded as a distinct clinical and genetic group and we suggest that they should be called *limb-girdle muscular dystrophy*. Leaving aside certain clinical characteristics which may be added later, we feel that the cardinal features of this type are (*a*) onset usually late in the first or in the second or third decade but sometimes in middle age, (*b*) commencement of muscular weakness in either the shoulder or pelvic girdle, (*c*) transmission usually via an autosomal recessive gene, (*d*) a relatively slow course which nevertheless leads to severe disablement and often death before the normal age.

It can be concluded that the great majority of cases of muscular dystrophy can be classified into three main groups, the Duchenne, facioscapulohumeral and limb-girdle types. Although these divisions correspond broadly to those used by Bell, we believe them to be more clearly defined. In all of our families the condition " bred true "; our observations indicate that the three forms are clinically and genetically distinct and we cannot support Bell's suggestion that " the same main gene can produce any of the three types." As we have mentioned already, this misconception probably arose from inaccuracies in some of the published reports which she reviewed.

The classification of dystrophia myotonica and related disorders.—We do not propose to dwell upon this subject as we cannot hope, from our relatively limited experience, to consider it so exhaustively as have Maas and Paterson (1939, 1950). However, brief consideration is essential for the accurate classification of our cases. Bell (1947) has expressed the view that myotonia congenita, paramyotonia and dystrophia myotonica are independent and distinct disorders and has quoted in support of this view Birt's (1908) description of myotonia congenita as it affected members of his family. She suggested that any observer reading this account would inevitably conclude that the natural history of this condition is entirely different from that of dystrophia myotonica. She also mentioned that the occurrence of myotonia only on exposure to cold (as in paramyotonia) seemed to distinguish this condition clearly from the other types. A dominant form of inheritance has been observed in families of all three types, although it is true that the association of other genetically-determined abnormalities such as cataract in the dystrophia myotonica families, together with the natural history of cases of the three conditions have led many geneticists (e.g. Penrose, 1948) to assume that they are distinct. Despite this assumption it seems to us that in view of the similarity of the pattern of inheritance in all three, any distinction between them must

be made primarily on clinical grounds. Maas and Paterson (1939, 1950) have advanced numerous arguments for believing that the three syndromes are but variations of a single disease process. They point out that in many cases diagnosed by neurologists as myotonia congenita they discovered minimal dystrophic features on careful examination: in their view the syndrome of myotonia congenita is merely an early form of dystrophia myotonica, and paramyotonia is another variant. Whereas in certain families myotonia is the predominant symptom for very many years before dystrophic signs develop, and even then the evidence of dystrophia may be minimal, in others the full-blown picture of dystrophia myotonica develops early. These discrepancies are, they believe, merely due to variations in expression of the same main gene or group of genes. Despite the evidence produced by Maas and Paterson there is no measure of general agreement on this problem and in their 1950 paper they give one list of authors who believe the conditions to be the same, and another list, equally long, of workers who consider them different.

In our study we have obtained information concerning 23 cases (15 examined personally), in 17 sibships of 12 families which would be classified traditionally as dystrophia myotonica. We have also discovered 8 cases, of which we have examined 6, falling under the heading of myotonia congenita and occurring in 5 sibships of 3 families. No cases of paramyotonia have come to our notice. All cases classified as dystrophia myotonica showed features of the fully developed disease and in these families another 5 members who could not be examined were possibly affected, while 5 apparently unaffected individuals had had cataracts and another 2 were mentally defective. In 2 of the myotonia congenita families all of the patients were under the age of 25; none of them showed any overt dystrophic features, but on slit-lamp examination one man of 24 was found to have very early changes in the posterior lamella of the lens of one eye. In the third family diagnosed as myotonia congenita the only affected individual who was available for examination was a woman who was first seen in the Royal Victoria Infirmary at the age of 12, when she showed generalized muscular hypertrophy and myotonia and was regarded as a typical case. When seen by us at the age of 24 she still showed muscular hypertrophy and severe myotonia in the limbs and trunk with no peripheral myopathy, but there was some wasting of both sternomastoids, slight facial weakness, impairment of ocular movements in all directions and bilateral early cataracts. This case alone gives ample support for the thesis advanced by Maas and Paterson and the evidence for essential identity of the three conditions seems irrefutable. However, we would not agree entirely with their suggestion that the condition, with all its

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variations, should be called Thomsen's disease, in view of the long association of this name with the myotonia congenita syndrome. Furthermore, it seems to us that there is ample evidence to show that the course of the disorder is usually much more benign in those patients whose disability is entirely due to the myotonia for many years; even though dystrophic features may eventually develop in such individuals they often appear to live to a normal span without becoming seriously disabled (Nissen, 1923; Thomasen, 1948). On the other hand, patients in whom the full-blown clinical picture of dystrophia myotonica develops early often progress to severe disability and death in middle life (Bell, 1947). Cases with paramyotonia are very rare, so that it is difficult to assess the natural history of this syndrome; however it seems that they are comparable to those of myotonia congenita save for the relationship to cold (Eulenburg, 1886).

As we have pointed out in connexion with the muscular dystrophies, the main purpose of classification of cases is in order to assess the prognosis; for this reason we feel that it is justifiable to consider myotonia congenita, dystrophia myotonica and probably paramyotonia as separate clinical syndromes occurring within the structure of a single disease process. It is probably justifiable to refer to the whole entity as "*the myotonic syndrome*" and to describe its different modes of presentation as the myotonia congenita, paramyotonia and dystrophia myotonica forms.

Material and Methods

In reviewing our suggested classification of the myopathies we have had to refer to certain clinical features and details of inheritance which we have observed in a series of cases. We have mentioned that the genetic aspects of this group of disorders will be treated in detail in a subsequent communication, when full pedigrees of the families will be given. We now propose to review briefly the clinical features and natural history of the disease in the cases which we have examined personally, in order to substantiate the groupings we have proposed. The results of a controlled trial of treatment in these cases will also be given.

Our series consists of 105 cases; 84 were "pure" muscular dystrophies and of these 48 were of the Duchenne type, 18 limb-girdle, 15 facioscapulohumeral, 2 distal and 1 ocular. The remaining 21 patients exhibited the myotonic syndrome and of these 15 were of the dystrophia myotonica type, and 6 myotonia congenita. We have not included in this series several highly atypical cases of myopathy (e.g. myasthenic and unusual congenital forms) as we propose to describe these rare cases in a communication on the "borderland of myopathy"; nor have we included the benign child-

hood cases in which recovery occurred since these will be described in full in a later paper (Walton and Nattrass, 1954).

We believe that our series approaches complete ascertainment of the cases of myopathy in Northumberland and Durham. We began by interviewing the patients in this area who were notified to the Ministry of Health when a Muscular Dystrophy Association was formed in 1949; later an attempt was made to trace all cases figuring in the in-patient and out-patient records of the Royal Victoria Infirmary and of other hospitals in the area during the last twenty years. In addition, circulars were sent to all physicians, orthopædic surgeons and ophthalmologists in the area setting out the aims of the investigation and asking them to notify cases. There was a gratifying response to this appeal, while other cases were referred by general practitioners who were also told of this study. All patients were first interviewed and examined in detail by one of us (J. N. W.) as were available members of their families. The patients were later admitted to hospital for two or three days for investigation (electromyography, muscle biopsy, urine chemistry, etc.), and for independent clinical assessment (F. J. N.), before beginning treatment. At this stage measurements of the degree of muscle wasting were made, the ability of the patient to carry out certain standard movements was noted, and the power of individual muscles and muscle groups was estimated clinically according to the methods described in the Medical Research Council pamphlet "Aids to the investigation of peripheral nerve injuries" (1943). Ergometric methods were attempted but were not found to be satisfactory.

In presenting the results of this investigation all significant details of the clinical findings and course have been analysed by the "Hollerith" system, while the results of treatment in the various groups have been compared statistically.

The Clinical Features and Natural History of the Myopathies

In the interests of brevity the work of previous authors will not be referred to in the ensuing section, which will be devoted entirely to describing the findings in our cases, particularly in so far as they relate to our proposed classification. Valuable accounts of the clinical manifestations of the muscular dystrophies will be found in the works of Sjövall (1936), Bell (1943), Shank, Gilder and Hoagland (1944), Tyler and Stephens (1950, 1951), and Levison (1951), though it is difficult to improve upon the word-pictures given by Duchenne (1868), Erb (1894) and Gowers (1879). Of the recent clinical descriptions of the myotonic syndrome, probably the most instructive are those of Martin (1947) and Thomasen (1948) but

again they cannot surpass the early accounts of Thomsen (1876) and Batten and Gibb (1909).

(1) *The Duchenne Type of Muscular Dystrophy.*

Of the 48 cases in this group, 45 were males and 3 females; 25 of the cases, including all the females, were isolated, while the remainder had affected siblings or other relatives. As already pointed out, the mode of inheritance was invariably compatible with transmission via a sex-linked recessive gene.

Age of onset.—The age at which the first symptom or sign of muscular abnormality became evident was noted in all cases and this information is tabulated in Table I.

TABLE I.—THE AGE OF ONSET OF THE DUCHENNE TYPE MUSCULAR DYSTROPHY IN 48 CASES

Age of onset in years	*Number of cases*
0–1	9
1–2	11
2–3	2
3–4	2
4–5	6
5–6	5
6–7	2
7–8	0
8–9	3
9–10	1
10–11	2
11–12	1
14–15	2
17–18	1
26	1
Total	48

It will be seen from Table I that the disease began before the age of 4 years in half the cases; it started most often in the second year, although in at least 9 cases (19 per cent) the mothers detected some abnormality in the first year of life. In 11 cases (6 occurring in 2 families) the onset was delayed until after the age of 8 years, and in one it gave no sign of its presence until the patient was aged 26.

Precipitating factors.—In 3 cases symptoms of the disease were first noted after an exanthem, in 1 after tonsillitis and in 2 after a fall.

Despite much that has been written on the provocation of muscular dystrophy by exogenous factors it seems clear that all of these factors act simply by bringing to light muscular weakness which was previously latent.

Symptomatology.—The presenting symptoms in these cases are given in Table II.

TABLE II.—THE FIRST SYMPTOM IN 48 CASES OF DUCHENNE TYPE MUSCULAR DYSTROPHY

Symptom	*Number of cases*
"Never normal from birth"	9
Unable to walk at normal age	3
Abnormal gait	13
Slowness and clumsiness in walking or running	12
Difficulty in climbing stairs	3
Difficulty in rising from the floor or from low chairs	2
Frequent falling	6
Total	48

The children who, according to their mothers, were "never normal from birth" often had difficulty in turning over in their cots and did not sit or stand at the normal age. They often walked late and when they did so they were clumsy or walked abnormally, tending to fall very frequently. Other symptoms, developing as the disease progressed, are listed in Table III.

TABLE III.—THE SYMPTOMS OF THE DUCHENNE TYPE OF MUSCULAR DYSTROPHY

Symptom	*Number of cases*
Delay in beginning to walk	12
Difficulty or clumsiness in walking	48
Dragging of the feet	25
Difficulty in climbing stairs	42
Never able to climb stairs	6
Frequent falling. "Knees give way"	48
Waddling gait	46
"Walking on the toes"	25
Rising from floor by "climbing up legs"	43
Difficulty in rising from the floor without actually "climbing up legs"	5
Difficulty in getting out of low chairs	44
Swelling of the calves	40
Pain in the legs on walking	9
Pain in the calves at rest	1
Pain in the back	5
Difficulty in raising arms above shoulders	43
Shoulders "hunched forwards"	10
Weakness of elbow flexion	34
Weakness of hands	5
Muscular fatigability (indefinite)	5
Weak cough	2
Excessive gain in weight	13
Curvature of spine	31
Progressive deformity	8

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Detailed analysis of these symptoms can conveniently be deferred until we have considered the available information concerning the course of the disease and our physical findings, so that we may endeavour to describe a composite clinical picture of this form of the disease. However it is worth noting at this stage that 10 patients complained of pain in the legs (usually in the calves), and another 5 had low back pain, probably owing to the abnormal strain on the spinous ligaments as a result of muscular weakness. This point is stressed since pain is not regarded as a common clinical feature of this disorder.

Course of the disease.—The duration of symptoms at the time when the cases were first observed is given in Table IV.

TABLE IV.—DURATION OF SYMPTOMS AT TIME OF OBSERVATION

Duration	*Number of cases*
Under 1 year	0
1–2 years	1
2–3 years	2
3–6 years	13
6–10 years	9
10–20 years	17
20–30 years	6
Total	48

It will be noted that in most cases the disease had been in progress for between three and twenty years. About half of these patients were severely disabled, as were all of those in whom the condition had lasted

TABLE V.—THE STATE OF THE PATIENTS AT THE TIME OF EXAMINATION AND IMPORTANT FEATURES OF THE COURSE OF THE DISEASE

Clinical state	*No. of cases*	*The course of the disease*	*No. of cases*
Ambulant	18	Steady deterioration	45
Can walk a few steps with great difficulty	5	Periods of apparent temporary arrest	3
Unable to walk; confined to wheelchair	22	Unable to walk within 5 years of onset	8
Grossly deformed and bed-ridden	3	Unable to walk within 5–10 years of onset	10
Still at school	12	Unable to walk within 10–20 years of onset	10
Unable to attend school ...	13	Unable to walk within 20–25 years of onset	5
Doing manual work	2	Able to walk after disease in progress 10 years	8
Doing professional work ...	1	Able to walk after disease in progress 20 years	5
Clerical work	2	Able to walk after disease in progress 25 years	0
Skilled sedentary work ...	2		
Unable to work	16		

more than twenty years. The clinical state of the patients at the time of examination and important features concerning the course of the disease are given in Table V.

In all 48 cases the symptoms indicated clearly that muscular weakness began in the pelvic girdle or lower limbs. The interval elapsing before there was overt evidence of upper limb involvement is shown in Table VI.

TABLE VI.—INTERVAL ELAPSING AFTER ONSET BEFORE THERE WAS DEFINITE EVIDENCE OF UPPER LIMB INVOLVEMENT

Duration of interval	*Number of cases*
1–2 years	5
3 years	11
4–5 years	12
6–7 years	9
8–10 years	5
11–15 years	3
Total	45

It may be of value at this stage to consider certain incidents in the course of the disease which occurred in a proportion of the patients.

Fractures of long bones as a result of minimal trauma occurred in 4 cases; in all 4 the femur was the bone concerned although one patient had also suffered a fracture of the humerus.

Exanthemata or other conditions requiring nursing in bed occurred in 24 patients during the course of the disease; 8 had shown a marked exacerbation of muscular weakness after these episodes and this deterioration was permanent in 7 cases and temporary in 1. Another 13 patients had deteriorated slightly afterwards and in 10 of these the increase in disability was permanent. It seems evident that any patient with this form of muscular dystrophy who is kept in bed runs the risk of deterioration. In general, however, the pattern of morbidity from intercurrent illness in this group of patients was not different from that to be expected in a comparable group of normal individuals.

Age at death.—4 of our patients have died from inanition or respiratory infections whilst under observation and at the time 3 were aged 15 and the other 18 years. In the families which contained affected individuals in the same and previous generations, 6 cases (not observed by us) had died at the respective ages of 3½, 14, 18, 22, 40 and 49 years.

Physical findings.—It was remarkable how often the appearance of the patient gave an impression of *mental backwardness,* an impression which was not substantiated by testing. At least 10 patients had a peculiarly coarse, "brutish" appearance, while another 6 were dull, unresponsive

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and monosyllabic. Yet no patient was mentally defective, only 4 were slightly backward, and psychometric testing in 6 who looked particularly dull showed them to be of above normal intelligence. Probably much of the impression of mental retardation can be attributed to loss of education or perhaps to the way in which these patients react to their physical disability.

In 36 cases the *state of general nutrition* was normal, but 12 were obese, 5 to a gross extent, and 1 showed multiple cutaneous striæ. All 12 obese patients had been severely disabled for some time, and although puberty had been delayed in 3 cases, all the remainder showed normal sexual development. Indeed, immaturity was not a significant feature of these patients and none showed any striking evidence of *endocrine abnormality*.

An unusual degree of *bluish mottling of the skin*, particularly of the lower extremities, was observed in 6 cases and 3 patients had *macroglossia*. A persistent *tachycardia* (pulse-rate 100 per minute with the patient at rest) was present in 41 cases; another 2, who were unable to walk, showed marked pitting œdema of the lower extremities, but no other significant abnormalities were found in the cardiovascular system, save in one patient who had a congenital subaortic stenosis. The blood pressure was within normal limits in all.

All other significant physical findings were in the muscular and skeletal systems; in no case was there any clinical evidence of associated disease or involvement of the central nervous system. As already mentioned (Table V), only 23 patients were able to walk at the time of examination. In 2 early cases the *gait* showed no detectable abnormality, but in the other 21 it was typically waddling in character, and all patients showed protuberance of the abdomen with accentuation of the lumbar lordosis. In 16 of the cases there was also evidence of foot-drop and inversion of the feet, so that the patient walked on his toes, with circumduction of the feet: this feature, combined with the rolling movement of the trunk, gave a very characteristic picture. There was *difficulty in rising from the floor* in all cases and 16 patients " climbed up their legs " in the typical manner. Of the remaining 25 patients, 22 were confined to wheelchairs; 3 could stand though they were unable to walk, but the others showed variable degrees of progressive deformity. Finally, 3 patients were bedridden, grossly deformed, and almost totally immobile (e.g. fig. 4).

Pattern of muscular involvement.—In many textbooks there will be found the suggestion that in this disease the muscles first show pseudohypertrophy but later waste, and it is suggested that the pseudohypertrophied muscles are the weak ones. Our observations do not support this conception. We observed *pseudohypertrophy* with the characteristic firm

FIG. 4.—An advanced case of the Duchenne type of muscular dystrophy; this photograph illustrates the gross degree of deformity which may occur in the late stages of the disease.

yet doughy feeling on palpation and marked "ridging" on contraction, in the calf muscles of 28 patients at the time of examination. It will be remembered that 40 patients had shown some swelling of the calves in the course of their disease; in 12 of them it had disappeared before they were examined, while another 8 patients apparently had no muscular enlargement at any time. In 3 cases there was perhaps some enlargement of the hamstrings and glutei, while in another 2 the lateral vasti were unusually bulky; in only 2 cases was there any suggestion of pseudohypertrophy in the upper limbs, involving the deltoids and possibly the triceps. It must be pointed out that in a few other patients a number of muscles (e.g. deltoid) which are often spared in the early stages of the disease process "stood out" in comparison with their wasted neighbours, giving a false impression of enlargement.

Muscular weakness and wasting in the lower limbs usually began symmetrically in the iliopsoas, quadriceps, gluteus maximus, and sacrospinalis, and later spread to involve the adductors, anterior tibials, peronei, and lower and lateral abdominal muscles. In general, the abductors of the thigh, the hamstrings, gastrocnemius, soleus and tibialis posterior were spared by comparison; indeed it was an almost invariable observation that the calf muscles (despite the pseudohypertrophy) remained remarkably powerful until a very late stage of the disease. This general pattern was

followed by the great majority of cases, although 2 were somewhat atypical in that the hamstrings were weaker than the quadriceps.

In the upper limbs, the disease process usually began in the trapezius, rhomboids, serratus anterior, latissimus dorsi and sternal portion of the pectoralis major, spreading later to involve the clavicular portion of pectoralis, biceps, brachioradialis and the extensors of the wrist and fingers. In comparison, the levator scapulæ, deltoid, the spinati, triceps, and the forearm and finger flexors were spared. The distribution was not, however, quite so invariable as in the lower limbs since 8 patients showed weakness and wasting of triceps at an early stage, and 5 of the deltoid and spinati, while in another 2 patients the forearm and finger flexors were weak in comparison with the extensors.

Although 2 patients were able to cough only very weakly, involvement of the intercostal muscles and diaphragm was not generally observed, although in the grossly deformed and immobile cases practically every muscle in the body which could be examined was weak. Indeed, 2 patients showed undoubted weakness of the orbicularis oris and orbicularis oculi; this facial weakness was only present at a very late stage and was certainly not sufficient to invalidate their classification as Duchenne type cases. In no case could we satisfy ourselves that a muscle was congenitally absent, a finding referred to by Batten (1909–10) and others.

The *deep tendon reflexes* were normal in 1 case only: in 6 patients all were absent, while in the remaining 41 the ankle-jerks were present but the other deep reflexes in all four limbs were absent (in 30 cases) or much depressed (11 cases). It is of interest that the reflexes were often greatly diminished before muscular wasting and weakness were severe.

Contractures were noted in 31 cases and involved the tendo Achillis and invertors of the foot in all of them (e.g. fig. 5), the hamstrings in 26, the biceps brachii in 16 and the pronators of the forearm in 13. These contractures clearly resulted partly from immobility of the limbs, which were constantly held in one position (e.g. knees flexed while sitting in a chair), and partly from the unopposed action of comparatively powerful muscles (gastrocnemius, tibialis posterior).

Skeletal changes.—The changes observed on radiological examination in 22 of these patients have been described in detail elsewhere (Walton and Warrick, 1954). They included narrowing of the shafts of the long bones (17 cases), abnormalities of the pelvic bones, scapulæ and clavicles (5 cases), scoliosis (9 cases, e.g. fig. 6), pes cavus (3 cases), and other deformities of the feet (3 cases). In the more advanced cases bony deformities were often very severe. It was concluded that the changes observed were due to disuse, to the absence of the stresses and strains imposed upon the bones by mus-

FIG. 5

FIG. 6

FIG. 5.—The leg of an advanced case of the Duchenne type, illustrating the characteristic equinovarus deformity resulting from muscular contractures. There is also marked mottling of the skin, not apparently the result of heat.

FIG. 6.—Gross scoliosis in a moderately advanced case of the Duchenne type.

cular attachments in the normal individual and to the development of abnormal postures of the body and extremities as a result of muscular weakness and/or contractures.

Conclusions.—It will be seen that this form of myopathy usually begins in the first 4 years of life, but sometimes the onset is delayed until the second or even the third decade. The condition is steadily progressive, periods of apparent arrest being a rarity; many patients become unable to walk within ten years, but a few remain ambulant for twenty years or longer. Death from inanition or respiratory infection usually occurs in the second decade but occasional patients may live until the forties. The progress of the disease may be exacerbated by a period of rest in bed. Muscular weakness always begins in the muscles of the pelvic girdle, giving the waddling gait, and in the quadriceps, weakness of which is responsible for the frequent falling, since "the knees give way" and also, in combination with weakness of the glutei, for the difficulty in climbing stairs. Weakness of the lumbar muscles and glutei is largely responsible for the characteristic method of rising from the floor. Walking "on the toes" results from weakness of the anterior tibial and peroneal muscles which causes the foot

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to assume a characteristic "talipes equinovarus" position. Muscles of the shoulder girdle are involved in practically all cases, though usually not until about three to five years afterwards. Pseudohypertrophy of the calf muscles occurs in about 80 per cent of cases, is uncommon in other lower limb muscles such as the hamstrings and glutei and is a rare finding in the upper limbs (deltoid and triceps). Swelling of the calves may disappear as the condition advances. Contractures of the less severely affected muscles commonly develop, and these, together with the muscular wasting, give rise to atrophy and deformity of the skeleton; bone atrophy may, in turn, lead to fractures as a result of slight trauma. Obesity occurs in a significant proportion of the immobile patients, but no other overt evidence of endocrine abnormality is common.

(2) *Facioscapulohumeral Muscular Dystrophy.*

We have observed personally 18 cases of this type, occurring in 4 families, but 3 of them came to light only recently, when we examined the relatives of our original patients: these 3 individuals (all abortive cases) believed themselves to be unaffected. This analysis will refer to the findings in the original 15 cases (3 male and 12 female) of which 10 were fully developed and 5 stationary or abortive.

Age of onset.—In 2 cases the disease began at 7 and 9 years respectively, in 10 it was first evident in the second decade and in 3 at the respective ages of 22, 26 and 27 years.

TABLE VII.—THE SYMPTOMATOLOGY OF FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Symptom	*Number of cases*
Presenting symptom	
Abnormality of facial movement	3
Difficulty in raising arms above shoulders	6
Drooping of one or both shoulders	6
Other symptoms	
Abnormality of facial movement	5
Difficulty in raising arms above shoulders	16
Drooping or hunching of shoulders	13
Inability to do hair	9
Asymmetrical weakness and wasting	2
Weakness of elbow flexion	8
Weakness of grip	2
Difficulty in walking	7
Difficulty in climbing stairs	6
Abnormal gait	7
Frequent falling	7
Difficulty in rising from floor	4
Pain in shoulders	1
Pain in legs on effort	1
Pain in back	2
Curvature of spine	9

In 13 cases there were no apparent *precipitating factors*, but muscular weakness was first evident in one case after a fall on the shoulder and in another after an attack of scarlet fever.

Symptomatology.—In Table VII we record first the presenting symptoms and secondly the other symptoms described by patients in this group.

It will be seen from Table VII that weakness of shoulder girdle muscles or an abnormal posture of the shoulders was usually the presenting symptom, except for 3 patients in whom an abnormal facial expression was observed. Although 9 patients had noticed some change in the shape of the back (usually accentuation of the lumbar lordosis), only 7 had symptoms clearly attributable to muscular weakness in the lower limbs. It is also of interest that only 5 patients were aware of facial weakness.

Course of the disease.—The duration of the disease at the time when we first observed these patients is given in Table VIII and certain important features of the course of the disease are correlated with the clinical state of the patients in Table IX.

The information given in Tables VIII and IX shows clearly the benign nature of this form of the disease. Even when the condition had been in progress for forty to fifty years patients could still walk quite well and the

TABLE VIII.—DURATION OF SYMPTOMS AT THE TIME OF OBSERVATION

Duration	*Number of cases*
5–10 years	4
10–20 years	2
20–30 years	5
30–40 years	2
47 years	1
53 years	1
Total	**15**

TABLE IX.—CERTAIN IMPORTANT FEATURES OF THE COURSE OF THE DISEASE CORRELATED WITH THE CLINICAL STATE OF THE PATIENTS AT THE TIME OF EXAMINATION

Clinical state	*No. of cases*	*Course of the disease*	*No. of cases*
Ambulant, can walk long distances	14	Slow steady deterioration ...	4
Ambulant but only able to walk short distances ...	1	Prolonged periods of apparent arrest	6
At school	1	Complete arrest	5
Unable to attend school ...	0	Able to walk well after 20 years	9
Heavy manual work	3	Able to walk well after 30 years	4
Clerical work	1	Able to walk well after 40 years	2
Skilled sedentary work ...	2		
Doing housework	7		
Unable to do useful work ...	1		

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majority were still able to do manual work or housework after more than twenty or thirty years. The only patient to be severely disabled was a girl aged 21 who walked very badly and was unable to work; in her case the disease was unusually severe. In many cases there had been periods of up to ten years when the disease had shown no clinical evidence of progression; in the 5 abortive cases there had been no increase in weakness for very many years (thirty-two years in one case).

It has already been pointed out (Table VII) that the first manifest symptoms of the disease were the result of involvement of muscles of the face or shoulder girdle. The interval elapsing before symptoms of pelvic girdle weakness came to light is noted in Table X.

TABLE X.—INTERVAL ELAPSING BEFORE THERE WAS DEFINITE EVIDENCE OF LOWER LIMB INVOLVEMENT

Duration of interval	*Number of cases*
7 years	1
10 years	1
13 years	1
15–20 years	2
20–25 years	2
Lower limbs not apparently involved	8

It is evident from Table X that this form of the disease may be limited to the face and shoulder girdle for many years before the lower limbs are involved. In all 5 abortive cases there were no symptoms or signs to suggest lower limb affection at any stage and this was true of three other patients, in whom the disease had been in progress for six, fifteen and twenty-two years respectively.

No patient in this group had sustained any *fractures* during the course of the disease; all but 2 of them had spent brief periods in bed owing to intercurrent illnesses, but only 1 (the severely disabled girl of 21 already referred to) had shown any significant deterioration as a result; in her case, the increase in muscular weakness, occurring after an attack of measles, was permanent.

Only 5 patients had received any drug treatment (nicotinic acid in 1 case, glycine and later α-tocopherol in 4 cases) and none had shown any significant change as a result. One patient had undergone a course of massage and exercises and another had had electrical treatment.

Age at death.—None of our personal patients have died whilst under observation. However, in previous generations of our families, affected individuals had died at 39 years (of cancer), at 65 years (heart attack) and at 82 years (natural causes). It seems clear that this form of muscular dystrophy is generally compatible with survival to old age.

Physical findings.—No mental defect or backwardness was observed in this group. None of the patients was unduly obese, nor did they show any evidence of endocrine abnormality. Apart from a moderate degree of hypertension in 4 patients (all over the age of 40), no significant cardiovascular changes were evident. Clinical evidence of disease of the central nervous system was not observed.

The *gait* was entirely normal in 6 patients, while 2 others walked with a mild accentuation of the lumbar lordosis but with no waddle. The remaining 7 all showed a marked increase in the lumbar curve (very severe in 2) and walked with a distinct waddle; there was also evidence of bilateral foot drop in 5 patients. The same 7 patients all had variable difficulty in rising from the floor and indeed 2 "climbed up their legs" like patients of the Duchenne type: they also found it difficult to rise from low chairs or to sit up from the supine position.

Pattern of muscular involvement.—Pseudohypertrophy of muscles was not observed in any of our 15 cases, although sparing of certain muscles, for instance the deltoid, sometimes gave a false impression of enlargement.

In considering the pattern of *muscular weakness and wasting* it will be convenient to consider separately the fully developed and abortive cases. In the *fully developed cases*, facial weakness was clearly evident in all; weakness of the orbicularis oculi gave rise to inability to close the eyes (fig. 7) while affection of the orbicularis oris gave the characteristic

FIG. 7.—Inability to close the eyes in facioscapulohumeral muscular dystrophy.

FIG. 8.—The characteristic "pout" of the lips in facioscapulohumeral muscular dystrophy.

"pouting" appearance of the lips (fig. 8), with inability to whistle or to blow out the cheeks. In 3 cases the lips could not be closed completely and this gave rise to dysarthria, since labials could not be pronounced. No patient showed clinical evidence of weakness of the extrinsic ocular muscles, and atrophy of the tongue was not observed.

The muscular involvement in the upper limbs was somewhat asymmetrical in 3 cases, being more severe on the right in right-handed individuals. The serrati, trapezii, rhomboids, latissimi and sternal portions of pectoralis major appeared to be involved first, and later the disease spread to involve the clavicular portions of the pectorals, the biceps, brachioradialis, and sometimes the extensors of the wrist and fingers. The levator scapulæ, deltoids and spinati were almost invariably spared for many years.

In the lower limbs, some signs of muscular weakness were evident in all 10 fully developed cases although only 7 patients had symptoms suggesting lower limb involvement. In general there was weakness of sacrospinalis, iliopsoas, gluteus maximus, quadriceps, adductors and the anterior tibial and peroneal muscles. However in 2 patients the proximal muscles were normal and weakness was limited to those of the anterior compartment of the legs, while in another 2 cases the hamstrings (which were in most cases powerful) were weaker than the quadriceps. The calf muscles were

invariably normal and only 3 patients showed weakness of the lower abdominals.

In the 5 *abortive cases* there was only minimal facial involvement, evident on very careful testing. At first sight facial movements were good, but 2 patients could not bury their eyelashes completely, while 4 found some difficulty in whistling. The remaining signs in these patients were limited to the upper limbs. All had drooping or an abnormal posture of one or other shoulder owing to involvement of the trapezius, and also weakness and wasting of the pectorals (figs. 9 and 10); 3 had slight winging

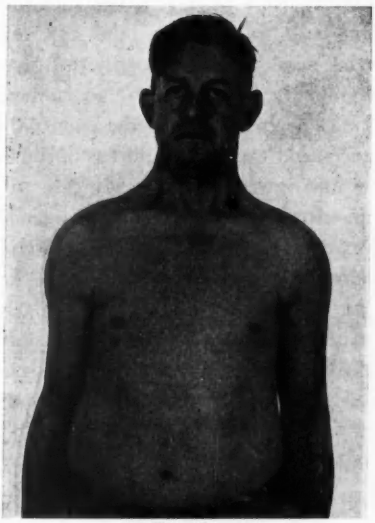

FIG. 9

FIG. 10

FIGS. 9 and 10.—An abortive case of facioscapulohumeral dystrophy; the pectoral muscles are wasted. Facial weakness, though present, is not evident in fig. 9 but the "pouting" lips are clearly seen in fig. 10, a photograph taken thirty-five years earlier. This patient is now working as a miner at the coal face at the age of 55.

of the scapulæ and 2 almost complete absence of the brachioradiales. No other muscles were involved: biceps, for instance, were powerful in all of them. There was no evidence to suggest that any of the affected muscles had been absent since birth.

The deep *tendon reflexes* were normal in 4 abortive cases, the radial jerks being absent in the other. All upper limb reflexes were absent in 5 of the fully developed cases and depressed in the others and the same was true of the knee-jerk; the ankle-jerk was active in every case.

One patient showed a slight degree of *contracture* of the tendo Achillis, but no contractures were seen in the others.

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Skeletal changes.—3 patients showed bone changes; all had narrowing of the shafts of the humeri, in 1 of them the scapula was small and decalcified and in another the pelvic bones were hypoplastic.

Conclusions.—The facioscapulohumeral form of myopathy may begin at any time during the first 30 years of life and though in general it is slowly progressive, abortive cases are often seen in which muscular involvement is limited to a few muscles and does not spread. Other patients show long periods of apparent arrest of the disease. In general, patients with this form of myopathy are able to live useful lives until a normal age and do not become totally disabled. Muscular weakness begins in the face and shoulder girdle muscles, giving characteristic "pouting" of the lips, and an immobile, unlined myopathic facies, combined with drooping or hunching forward of the shoulders and difficulty in raising the arms above the shoulders. In most of the fully developed cases the disease eventually spreads to the back muscles, causing accentuation of the lumbar lordosis, and to the muscles of the pelvic girdle and lower limbs, giving rise to a waddling gait, a tendency to fall and difficulty in climbing stairs or in rising from the floor. This spread to the lower limbs is often delayed for twenty to thirty years and it may never occur. The muscles which waste are roughly the same as those involved in the Duchenne type, despite the striking difference in rate of progress of the weakness. Pseudohypertrophy of muscles was not observed in our cases and appears to be very uncommon in this form of the disease, as are muscular contractures, while skeletal changes are also minimal.

(3) *Limb-girdle Muscular Dystrophy.*

Our personal series of cases of this type consists of 18 patients (11 males and 7 females) occurring in 18 families. In 2 of the families there had occurred at least 3 other affected individuals but all were dead when our study began.

Age of onset.—In 7 cases the disease began in the second decade, and in 4 in the third; another 4 patients first noted symptoms of muscular weakness between the ages of 30 and 40, 2 between 40 and 50 and 1 at the age of 53. 2 patients felt that the onset of the disease was related to trauma to the shoulder region, but the remainder did not describe any precipitating factors.

Symptomatology.—The presenting symptoms in these cases and other symptoms observed as the disease progressed are given in Table XI.

The information given in Table XI reveals that the initial symptoms could be attributed to shoulder-girdle weakness in 10 cases and to pelvic girdle involvement in 8.

TABLE XI.—THE SYMPTOMATOLOGY OF LIMB-GIRDLE MUSCULAR DYSTROPHY

Symptom	*Number of cases*
Presenting symptom	
Difficulty in raising arms above shoulders	10
Slowness or clumsiness of walking	3
Difficulty in climbing stairs	2
Difficulty in rising from chairs	1
Frequent falling	1
Inability to jump	1
Other symptoms	
Difficulty in raising arms above shoulders	18
Drooping or hunching of shoulders	9
Inability to do hair	10
Asymmetrical weakness and wasting	4
Weakness of elbow flexion	16
Weakness of grip	0
Difficulty in walking	13
Difficulty in climbing stairs	14
Abnormal gait	14
Frequent falling	12
Difficulty in rising from floor	10
Pain in shoulders	2
Pain in legs on effort	2
Pain in back	3
Curvature of spine	8
Facial weakness (unilateral facial palsy)	2

Course of the disease.—In Table XII the duration of symptoms at the time of observation is given and in Table XIII the clinical state of the patients is correlated with various important features of the course of the disease.

TABLE XII.—DURATION OF SYMPTOMS AT THE TIME OF OBSERVATION

Duration	*Number of cases*
10 months	1
8 months	1
4 years	1
5 years	1
6–10 years	2
10–20 years	7
20–30 years	3
30 years	2
Total	18

It is clear from Tables XII and XIII that this form of myopathy is much more benign in general than the Duchenne type, but the disease does not show quite the same uniform slowness of progression as does the facio-scapulohumeral variety. Indeed the natural history of the disease in these cases of limb-girdle myopathy shows much more variation than in the other

TABLE XIII.—THE CLINICAL STATE OF THE PATIENTS AT THE TIME OF OBSERVATION CORRELATED WITH SOME IMPORTANT FEATURES OF THE COURSE OF THE DISEASE

Clinical state	*No. of cases*	*Course of the disease*	*No. of cases*
Ambulant, can walk considerable distances	12	Slow steady deterioration ...	10
Can walk a few steps with considerable difficulty	4	Periods of apparent arrest ...	6
Unable to walk, confined to wheelchair	2	Complete arrest	2
		Unable to walk 20 years after onset	1
		Unable to walk 26 years after onset	1
Heavy manual work	4	Able to walk well after 20 years	6
Clerical work	3		
Skilled sedentary work ...	2		
Housework	4		
Unable to do useful work ...	5		

groups; whereas the course is sometimes as insidious as in the average facioscapulohumeral case, with periods of several years in which the disease fails to progress, in other cases weakness increases more rapidly and a significant proportion of the patients become unable to work and later unable to walk within twenty to thirty years of the onset. None of our patients in whom the disease has lasted over thirty years are still ambulant, but on the other hand, in 2 patients whose weakness started in the shoulder girdle there has been no apparent progress for twelve and eighteen years respectively and the lower limbs have not been involved. Despite the apparent lack of progress in these latter cases, muscular involvement in the upper extremities is more extensive and severe than in the abortive facioscapulohumeral cases. Although we have an impression that the disease may often be more benign when it begins in the upper limbs rather than in the lower, this is by no means invariable, since 2 of the patients who can walk only with considerable difficulty after fourteen and seventeen years respectively, first complained of shoulder girdle weakness.

We have mentioned that in 10 cases the condition began in the shoulder girdle and in 8 in the pelvic girdle. Table XIV gives the time taken for the disease to spread to the upper or lower limbs, as the case may be.

It is of interest to note that in 4 patients in whom the disease began in the upper limbs there had been no spread to the lower limbs at the time of observation. However, affection of the upper limbs was present at the time of observation in all patients whose weakness had first affected the lower extremities.

No *fractures* had occurred in any case of this group; although 16 patients had had intercurrent infections necessitating bed-rest, only 1 had shown slight permanent deterioration as a result.

TABLE XIV.—THE TIME TAKEN FOR THE DISEASE TO SPREAD FROM THE SHOULDER TO THE PELVIC GIRDLE OR VICE VERSA

Cases in which the shoulder girdle was first involved		*Cases in which the pelvic girdle was first involved*	
Duration of interval	*No. of cases*	*Duration of interval*	*No. of cases*
18 months	1	9 months	1
3– 4 years	1	18 months	1
5 years	1	2 years	1
10–15 years	2	4 years	2
18 years	1	6 years	1
Lower limbs not involved	4	14 years	1
		17 years	1
		Upper limbs not involved	0
Total	10	Total	8

Age at death.—None of our patients has died whilst under observation. However, in 2 of the families, apparently affected individuals had died at the respective ages of 47, 54 and 62 years. All of them had been severely disabled and unable to walk for some time; in 2 of them death was attributed to "pneumonia and muscular dystrophy," in the other to a heart attack. Although the number of cases is small, these observations suggest that death usually occurs earlier in the limb-girdle cases than in the facioscapulohumeral ones.

Physical findings.—In common with the facioscapulohumeral cases, no significant mental, endocrine, cardiovascular, or central nervous abnormalities were observed in our patients. 2 female patients and 2 males over middle age were somewhat obese, but many of the other patients were very thin.

The *gait* was entirely normal in 4 patients and in another 2 it could not be tested owing to inability to walk. One other patient showed only an increase in the lumbar curve but in the remaining 11, in addition to the accentuated lordosis, there was a distinct waddle, while 7 patients showed evidence of bilateral foot drop. The protuberant abdomen, the rolling movement of the trunk and the circumduction of the feet make the mode of walking characteristically "aldermanic," particularly in the middle-aged patient. All 11 patients with demonstrable pelvic girdle and quadriceps weakness had difficulty in rising from the floor and from chairs.

Pattern of muscular involvement.—One patient in this group showed some undoubted *pseudohypertrophy* of the lateral vasti; in one other the calves and in another the deltoids were rather bulky but were probably not outside normal limits. As in the facioscapulohumeral cases, such

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muscles as these which are not involved in the dystrophic process, at any rate in its early stages, often gave a false impression of enlargement.

The pattern of *muscular weakness and wasting* in these patients was very similar in the late stages in all cases, but in the beginning it depended upon the site of onset of the disease. 2 patients had each had a unilateral facial palsy since birth (fig. 11) but otherwise none of them showed facial weakness, nor did we observe affection of the extrinsic ocular muscles or of the tongue. In 2 cases the sternomastoids were weak and wasted.

When weakness began in the upper limbs, the muscles involved were similar to those affected in the facioscapulohumeral form (*vide supra*). Marked asymmetry of weakness and wasting was noted in 6 cases (e.g. fig. 11): indeed in 1 case there was severe wasting of the right arm and shoulder girdle while the left upper limb was almost normal. It is of interest that in these patients wasting was always more advanced in the limb which was used more often. Even the shoulder girdle muscles such as deltoid which were spared at first were eventually involved in many cases and these patients often showed severe wasting earlier than did the scapulohumeral ones (fig. 12). In addition to involvement of scapulo-

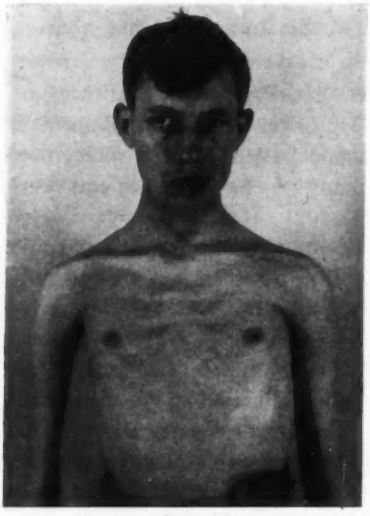

FIG. 11

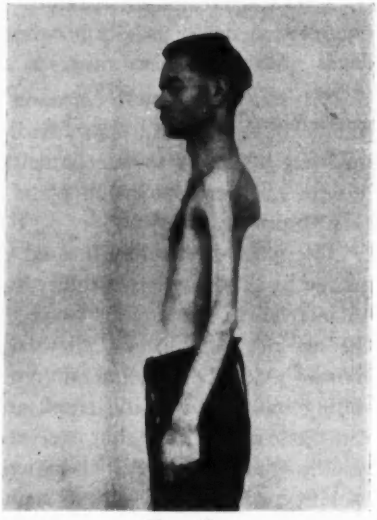

FIG. 12

FIG. 11.—Right facial palsy present since birth in a case of limb-girdle muscular dystrophy. Asymmetry of wasting in the upper limbs can also be seen, being much more severe on the right side.

FIG. 12.—Advanced muscular wasting with remarkably good functional capacity in a case of limb-girdle dystrophy.

humeral and pectoral muscles, the brachioradiales were affected in most cases, the wrist and finger extensors in several and the finger flexors in 4, while 1 patient showed severe wasting of small hand muscles at a late stage of his disease. In 7 of the 10 cases in this group there was variable evidence of spread to the lower limbs as described below.

Weakness beginning in the lower limbs again followed the usual pattern, affecting lumbar muscles, gluteus maximus, iliopsoas, quadriceps, adductors and anterior tibials. However, in 4 patients the hamstrings were affected earlier and became much weaker than the quadriceps, while in another 3 there was no involvement of muscles below the knee. Comparative sparing of the calf muscles was again general, and only 2 patients had weak lower abdominal muscles. All 8 patients in this group had affection of the upper limbs in variable degree. As in the other groups there was nothing to suggest congenital absence of muscles in any case.

The *deep tendon reflexes* were normal in 2 cases, the upper limb reflexes and knee-jerks were absent in 9 and depressed in 4 cases; in the other 3 patients the upper limb reflexes were absent and those in the lower limbs were present; the ankle-jerks were present in all cases.

Contractures of the tendo Achillis and of the hamstrings were observed in the 2 patients who were unable to walk, but in none of the other patients.

Skeletal changes were discovered in only 2 of the 8 patients who were examined radiographically. One showed some narrowing of the shaft of one humerus, the other some atrophy of clavicles and scapulæ.

Conclusions.—The limb-girdle form of myopathy is more variable in its clinical manifestations than either of the forms previously considered. The disease usually begins in the second or third decade but can probably begin at any time after the first 5 years of life; it is usually slowly progressive but there may be prolonged periods of clinical arrest. Though sometimes compatible with survival to old age, in general it produces severe disability within twenty to thirty years of the onset. Abortive cases are very uncommon. When it begins in the second decade many patients are likely to die in middle age.

Muscular weakness may begin first in the upper limbs and often affects more severely the arm which the patient uses most often. Difficulty in raising the arm and in lifting objects is experienced. In other cases the pelvic girdle is first involved, causing a waddling gait, falling, difficulty in climbing stairs and in rising from the floor. Most patients whose disease begins in the upper limbs develop signs of pelvic girdle weakness within twenty years, though in a few the disease may remain limited to the upper

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limbs. All patients with primary pelvic girdle weakness appear to develop upper limb weakness within twenty years. The muscles involved are similar to those which waste in the other forms of myopathy. Pseudohypertrophy is very uncommon, contractures only develop at a late stage and skeletal changes are relatively insignificant.

(4) *Distal Myopathy.*

We have observed 2 cases of this type, both males; 1 was isolated but the other remarked that his father and 2 paternal aunts had " something wrong with their legs and arms " and had considerable difficulty in walking. Unfortunately the patient had not seen these relatives for some years and they were not available for examination but all of them were still alive and over 60 years of age.

In our 2 cases first symptoms of the disease were noted at the respective ages of 21 and 23 years and consisted of clumsiness in walking and running, with frequent tripping and falling. Subsequently both patients developed weakness and clumsiness of the hands and forearms and later still, difficulty in climbing stairs and in lifting the arms above the shoulders. When first observed, after the disease had been in progress for nine and six years respectively, neither patient was able to walk, though each could stand unsupported; one was working as a draughtsman, the other as a research chemist.

The pattern of muscular weakness and wasting was virtually identical in the 2 cases. There was almost complete inability to move the toes and feet in any direction and the anterior tibial, peronei and calf muscles were severely wasted. The quadriceps, adductors and particularly the hamstrings were also affected, though less severely. In the upper limbs there was marked weakness and wasting of all small hand muscles, particularly the abductor pollicis which was virtually absent. The flexors and extensors of the wrists and fingers were also weak, as were the biceps, triceps and brachioradiales. The serrati, latissimi and pectorals were also involved, though to a lesser extent. All deep tendon reflexes were absent. Despite the severe peripheral weakness and wasting of muscles there were no contractures, presumably owing to the fact that agonists and antagonists had atrophied almost equally. The sternomastoids and facial muscles were not involved, nor did these patients show any other features at all suggestive of dystrophia myotonica.

Our limited experience of this form of myopathy does not allow us to make generalizations, but in our cases the disease began in the third decade and was rapidly progressive; muscular involvement clearly began in the distal muscles of the arms and legs but later spread to the same

proximal muscles which are involved in the other forms of myopathy. Despite the latter point of similarity, we are confident that this form of the disease is a distinct entity.

(5) *Ocular Myopathy.*

A single case of this type in a man of 23 years with no affection of other members of his family has come to our notice. The patient had experienced progressive symmetrical drooping of the eyelids for five years but had no other symptoms. On examination he showed very marked bilateral ptosis with compensatory wrinkling of the forehead. There was symmetrical impairment of ocular movement (less than 5 degrees) in all directions. There was also marked weakness of both orbicularis oris muscles and of the right levator angulæ oris, while abduction of the right shoulder was weaker than the left and the right tibialis anterior muscle was weak and wasted. An electromyogram from the right orbicularis oris and one from the right tibialis anterior gave a characteristically myopathic pattern.

(6) *The Myotonic Syndrome.*

We have examined 15 cases of the fully developed dystrophia myotonica type, occurring in 12 families, and 6 falling under the heading of myotonia congenita, occurring in 3 families. No case of paramyotonia has come to our notice.

Dystrophia myotonica.—Of our 15 cases, 8 were males and 7 females. In 3 of the families we obtained clear evidence of a dominant mode of transmission of the disease, but in the remaining families we were unable to examine the members of previous generations, some of whom may well have been affected.

Age of onset.—The age of onset of the disease in these cases is given in Table XV.

TABLE XV.—THE AGE OF ONSET OF DYSTROPHIA MYOTONICA IN 15 CASES

Age of onset	*Number of cases*
Soon after birth	1
7 years	1
14 years	1
20–30 years	5
30–40 years	4
40–50 years	2
62 years	1
Total	15

The age given in each case is that at which the patient was noted to be abnormal by his or her parents or else that at which he or she was first

aware that something was wrong. It is clear that this form of the disease may first come to light at any age though it most often does so in the third or fourth decades.

Symptomatology.—The presenting symptoms in these cases are given in Table XVI and other symptoms developing subsequently are recorded in Table XVII.

TABLE XVI.—THE PRESENTING SYMPTOM IN 15 CASES OF DYSTROPHIA MYOTONICA

Symptom	*Number of cases*
Never normal from birth owing to muscular stiffness and mental defect	1
Muscular stiffness (myotonia)	5
Frequent falling	4
Difficulty in walking	1
Abnormal facial expression	3
Drooping of the eyelids	1
Total	15

TABLE XVII.—THE SYMPTOMATOLOGY OF DYSTROPHIA MYOTONICA

Symptom	*Number of cases*
Stiffness of limb muscles (myotonia)	13
Stiffness of tongue (myotonia)	3
Difficulty in walking	11
Dragging of the feet	14
Difficulty in climbing stairs	11
Frequent tripping and falling	14
Difficulty in rising from the floor	10
Pain in the legs on walking	4
Alteration in facial expression	3
Drooping of the eyelids	10
Weakness of neck muscles (difficulty in raising head from pillow)	10
Difficulty in raising arms above shoulders	4
Weakness of elbow flexion	9
Weakness of grip	13
Pain in the back	2
Dysarthria	9
Loss of libido	7
Impotence	5
Visual deterioration	8
Loss of weight	7
Profuse perspiration	6
Mental defect	1

It will be seen from Table XVII that the great majority of the patients had symptoms attributable to peripheral weakness of the limbs. Tripping and falling were due to foot drop in most cases, though it is of interest to note that several patients had difficulty in climbing stairs and in rising

from the floor; these symptoms were due almost entirely to involvement of the quadriceps, the first of the proximal muscles to be involved. The fact that only 3 patients were aware of facial weakness, though 10 had noted drooping of the eyelids, is also of interest.

It is worth considering the symptom of myotonia in some detail. At least 2 patients were aware of myotonia of practically all the skeletal muscles; 3 patients realized that their tongues were unusually stiff at times but in the other 8 patients who were aware of this symptom it was manifest solely as difficulty in relaxing the grip. Myotonia was noted early in the course of the disease in 9 cases but much later in 4; in 1 patient it occurred only in the cold weather and in 11 others it was made much worse by cold.

Course of the disease.—When we first observed our patients 1 had experienced symptoms for three years, 1 for five years and another for eight years, while 7 had suffered from the condition for between ten and twenty years and 5 for twenty to thirty years.

The clinical state of the patients at the time of examination is correlated with certain important features of the course of the disease in Table XVIII.

TABLE XVIII.—THE STATE OF THE PATIENTS AT THE TIME OF EXAMINATION AND SOME IMPORTANT FEATURES OF THE DISEASE

State of the patients	*No. of cases*	*The course of the disease*	*No. of cases*
Ambulant	7	Steady deterioration	15
Can walk short distances with great difficulty	6	Periods of apparent arrest ...	0
Unable to walk; in a wheel chair	2	Unable to walk after 18 years	1
		Unable to walk after 21 years	1
At school	1	Walking well after 10 years	5
Doing manual work	1	Walking well after 20 years	1
Clerical work	1		
Skilled sedentary work ...	1		
Housework	3		
Unable to do useful work ...	8		

It is clear from Table XVIII that this disease is steadily progressive and does not show periods of arrest such as are observed in the limb-girdle and facioscapulohumeral forms of myopathy. Most patients become seriously disabled and unable to work within twenty years of the onset.

Affection of the upper and lower limbs appears to be virtually simultaneous in this condition; although in 8 patients the first symptoms could be attributed to changes in the upper limbs, the legs were clearly affected in most of them within two years and in all within five. Similar progress was evident in the 7 cases whose disease appeared to begin in the legs.

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Fractures of the limbs and deterioration after intercurrent illnesses were not observed. 8 had received quinine *treatment*, but in only 2 of them was the myotonia improved significantly by this remedy.

8 of the patients were married and 7 had children, but no offspring had been born to any of the patients after the disease had been in progress for more than ten years.

Age at death.—One of our patients died whilst under observation, at the age of 58 years, while 3 affected siblings of one of our other cases died at 49, 42 and 38 years respectively. In previous generations of our families affected individuals had died at 61, 69 and 70 years respectively.

Physical findings.—Only 7 of our patients were of normal *mentality* and intelligence. A female patient of 14 years had a mental age of 7 and another patient was of subnormal intelligence (I.Q.=85). 3 other individuals showed evidence of early dementia and another 3 were themselves aware of slow deterioration in memory and intellect.

In 6 patients the state of *general nutrition* was normal and 2 were obese, but the other 7 patients were all thin and wasted. All but 1 of the male patients showed some *frontal baldness* and 6 had definite *testicular atrophy*.

Advanced degrees of cataract could be observed with an ophthalmoscope in 6 patients and the other 9 all showed lens changes on slit-lamp examination.

Profuse *perspiration*, particularly of the face and hands, was noted in 7 cases.

None of the patients showed evidence of congestive heart failure; 3 were hypertensive but there were no other significant physical signs on examination of the cardiovascular system. No evidence of central nervous system involvement was observed in any case.

The *gait* was normal in one of the 13 patients who could walk; the others all showed bilateral foot drop to a variable extent and 3 also had a distinct waddle.

Pattern of muscular involvement.—Muscular *hypertrophy* was evident in one case only, a man of 35 years whose proximal muscles in both the upper and lower limbs were very powerful and bulky and showed clear myotonia on mechanical stimulation. This patient had undoubted peripheral wasting in marked contrast to the appearance of his proximal muscles. Myotonia was demonstrable in the hand and forearm muscles and in the tongue in 13 of the total of 15 cases; in 3 of these, including the case referred to above, a considerable proportion of the skeletal muscles revealed this phenomenon. In the 2 cases which showed no clinical

myotonia even after cooling, the characteristic myotonic discharge was recorded from the forearm flexors during electromyography.

Muscular *weakness and wasting* in these patients followed the accepted pattern. There was ptosis in 14 cases and 6 patients had symmetrical involvement of the extrinsic ocular muscles: 3 of them had only a few degrees of ocular movement in any direction, while similar but less severe impairment was apparent in the others. In all 15 cases the facies could be described as myopathic, and every patient had weakness of the orbicularis oculi and of orbicularis oris. 14 patients were dysarthric; in 5 this could probably be attributed to facial weakness and in 9 to myotonia of the tongue. Variable involvement of the masseters, temporales and sternomastoids was observed in all cases.

All 15 patients showed signs of a peripheral myopathy affecting all four limbs and in various stages of development. The small hand muscles were spared by the myopathic process until a late stage of the disease; weakness began and wasting followed in the long extensors and flexors of the wrist and fingers in the upper limbs and in the tibialis anterior, peronei and calf muscles in the lower. In 4 cases the atrophy in the lower extremities was so advanced that practically no voluntary movement of the feet and toes was possible. Weakness had spread proximally in 11 cases involving biceps and triceps in the upper limbs and quadriceps and hamstrings in the lower, while 5 patients also showed signs of involvement of deltoids, pectorals and serrati. Hence, although affection of the limbs invariably begins peripherally, proximal muscles are also involved in a considerable proportion of cases.

The deep *tendon reflexes* were normal in 2 early cases while all were absent in 4 patients whose disease was advanced. In the remainder the radial and ankle jerks were absent while the biceps, triceps and knee jerks were depressed to a variable extent.

2 patients showed some *contracture* of the tendo Achillis but none of the others showed significant muscular shortening.

Skeletal changes.—Radiographs of the limb bones and of the pelvis and chest were taken in 8 cases but revealed no significant changes. Radiographs of the skull were taken in all cases and the changes observed have been described elsewhere (Walton and Warrick, 1954); in these cases the sella turcica was usually smaller and the vault of the skull thicker than in normal individuals.

Myotonia congenita.—We have observed 6 cases of this type occurring in 3 families; 1 patient was male, the other 5 were females, and they were aged respectively 9, 12, 18, 20, 24 and 24 years at the time of examination. In only one of the families were there similar cases in previous generations.

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In all cases the symptoms of which the patients complained could be entirely attributed to *myotonia*; they were all stiff and clumsy in walking or in using their hands. This stiffness was worse in cold weather and whenever they began to walk: they tended to stumble and fall a good deal but once they "got going" the muscles seemed to loosen and their walking improved. It is evident from the history that this symptom of myotonia affected practically all the skeletal muscles, 3 out of 6 siblings in family A were first noted to be abnormal soon after the age of 1 year, when they began to walk, but no significant abnormality was noted in the 2 sisters of family B until they went to school. The only patient in family C who was available for examination (her maternal grandmother and 1 maternal aunt were said to be very stiff, particularly in cold weather) was a woman of 24 years who was noted to be abnormal soon after birth: she seemed unable to grasp things as well as other babies and cried as if "her throat were stiff." She walked very badly and clumsily and in very cold weather was almost immobile. She was unable to walk upstairs until she was 5 years old and even now cannot run up an incline unless the weather is very warm: she always improves after exercise.

The muscular stiffness, and other symptoms attributable to myotonia, have persisted in all 6 patients, although 4 of them have improved appreciably with the passage of the years. No other significant symptoms have developed. None of our patients have died under observation, but the 2 sufferers in previous generations of family C died at 67 and 82 years respectively.

Well-marked generalized muscular hypertrophy and strikingly powerful muscles are evident in all 3 cases in family A; these features are most evident in the masseters, deltoids, biceps and quadriceps, and all show clearly defined myotonia on attempting to relax the grip and on mechanical stimulation of the muscles. The eldest patient in this family, a man of 24, has minimal posterior lamellar opacities in one lens on slit-lamp examination but otherwise none of the cases shows any dystrophic features.

The disease is relatively mild in the 2 sisters of family B; neither shows muscular hypertrophy, while myotonia of the forearm muscles and tongue, though clearly present, is difficult to elicit.

Muscular hypertrophy was clearly evident in the patient in family C at the age of 13 years (figs. 13 and 14) and is still well marked, particularly in the proximal limb muscles. She shows severe generalized myotonia, involving even the palatal and facial muscles and the platysma, but in addition there is undoubted weakness of the orbicularis oculi and the sternomastoids, ocular movement is grossly impaired in all directions (in addition

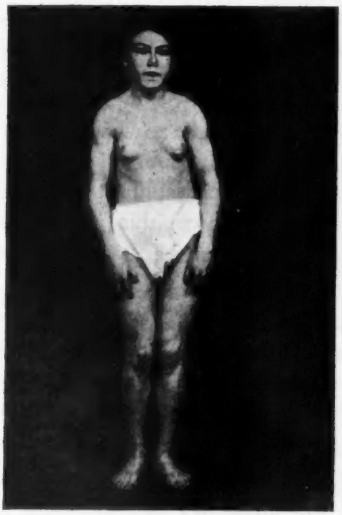

FIG. 13

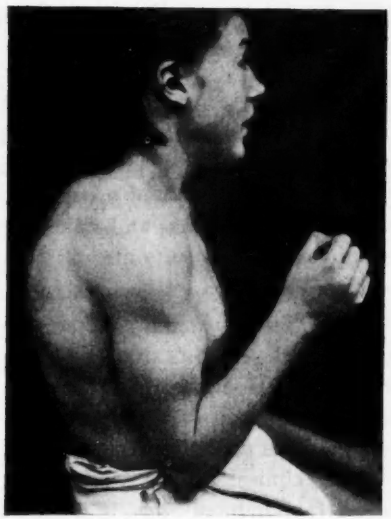

FIG. 14

FIGS. 13 and 14.—Generalized muscular hypertrophy in a girl aged 13 with "myotonia congenita."

FIG. 15.—The patient shown in figs. 13 and 14, now at the age of 25 years. There is bilateral ptosis, symmetrical impairment of ocular movement (the strabismus is concomitant in type) and weakness of facial muscles and of sternomastoids; the proximal limb muscles remain hypertrophied.

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to a concomitant strabismus) and there are well-defined opacities in both lenses. This patient is clearly developing well-defined dystrophic features (fig. 15).

Conclusions.—Our observations show that without any doubt dystrophic features may develop in a patient who has previously shown the typical clinical features of myotonia congenita; this fact supports the suggestion made by Maas and Paterson that cases of dystrophia myotonica and myotonia congenita are different manifestations of the same disease process.

Despite this evidence as to the essential identity of the two conditions it is nevertheless true that the average case of the one is very different from the average case of the other, so far as age of onset, clinical features and natural history are concerned. We feel, therefore, that it is justifiable to regard the two as separate syndromes and to classify patients according to these clinical groups, while realizing that certain cases are observed which cannot be adequately classified in this way since they fall into a transitional stage between the two.

The average patient with dystrophia myotonica begins in the third or fourth decade to suffer from muscular stiffness (myotonia) or difficulty in walking or weakness and clumsiness of the hands. Progressive disability occurs owing to a peripheral myopathy and is often joined as time passes, by impotence and frontal baldness (in the male), weakness of the neck owing to sternomastoid wasting, loss of weight, a change in facial expression (the myopathic facies) and sometimes impairment of ocular movement. Mental defect or backwardness and cataract are common in the patients and in their siblings. Within twenty years the patient is often severely disabled; he is usually unable to walk within twenty-five years of onset and death is common in middle life.

Whereas in many cases of the dystrophia myotonica type the symptom of myotonia is not noticed until other features of the disease are evident, and is then limited to the hand muscles and tongue, in the average patient with the myotonia congenita syndrome this symptom is apparent shortly after birth and affects the skeletal musculature generally. In patients of the latter type this symptom may be the entire cause of the patient's disability for many years before dystrophic features develop and even then the latter may be minimal. Although our patients in this category are too young for accurate assessment of the natural history it is clear from published work that many with this form of the disease live to old age without becoming seriously disabled. The same is probably true of paramyotonia, of which we have no personal experience.

Investigations

The results of electromyographic examination of the cases in this series have been described in detail elsewhere (Walton, 1952), while the *pathological changes* in specimens of muscle obtained by biopsy from 72 patients will be reviewed elsewhere by Dr. R. Schade.

Electrocardiograms were taken from all patients, utilizing the standard limb leads and CV4 in the cases of muscular dystrophy and a full range of chest and unipolar limb leads in the cases of dystrophia myotonica. In the limb-girdle, distal and ocular cases these recordings were normal and the same was true of the facioscapulohumeral group save for one patient in whom the P waves were unusually low and another whose tracings showed ischæmic changes. The electrocardiographic changes observed in the Duchenne type cases are recorded in Table XIX and those in cases of the dystrophia myotonica syndrome in Table XX.

Table XIX.—The Electrocardiographic Changes Observed in 48 Cases of Duchenne Type Muscular Dystrophy

	Normal	*Long PR interval*	*Wide QRS complex*	*Elevated ST segment*	*Depressed ST segment*	*Low P waves*	*Large P waves*	*Very tall T waves (blood K normal)*	*Deep Q1*	*Sharp inversion of T3*
Number of cases	36	0	2	1	1	2	1	1	3	1

Table XX.—The Electrocardiographic Changes Observed in 15 Cases of Dystrophia Myotonica

	Normal	*Prolonged PR interval*	*Abnormally long QRS*	*Elevated ST segment*	*Bundle branch block*	*Ischaemic changes*	*Abnormal V2 indicating a relative delay in right ventricular activation*	*Inverted T in V 5-6*
Number of cases	4	3	4	3	1	2	1	1

It will be seen that electrocardiographic changes indicating abnormality of the cardiac muscle were observed in a small proportion of the Duchenne type cases; these were practically all severely disabled cases of advanced disease. As is well recognized, the proportion of patients with dystrophia myotonica with abnormal electrocardiograms is very much

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greater. All 6 patients of the myotonia congenita type gave normal tracings, but, as already mentioned, they were comparatively young.

No detailed biochemical investigations were carried out on our patients in view of the exhaustive metabolic studies performed by Milhorat and his co-workers and by Tyler and Perkoff (1951). However, specimens of urine from 89 cases were examined for the presence of ribose by the technique described by Orr and Minot (1952). These authors discovered *ribosuria* in samples of urine from 26 cases of muscular dystrophy, 6 of dystrophia myotonica, 5 of myotonia congenita and 3 of amyotonia congenita, and the test was invariably negative in specimens from patients with progressive muscular atrophy and other forms of neuromuscular disease. In our cases the test gave a positive result in 10 of 46 cases of Duchenne type dystrophy, in none of 14 cases of the facioscapulohumeral type, in one of 16 limb-girdle cases and in 1 of 13 patients with dystrophia myotonica. Since the test gave a positive result when specimens from 2 cases of motor neurone disease were examined it is clearly of no value for diagnostic purposes. Similar conclusions have been reached by Matthews and Burne (1953) who utilized a sensitive paper chromatographic technique for the detection of ribose.

Treatment

From time to time reports have appeared of improvement occurring in cases of muscular dystrophy as a result of many diverse remedies including aminoacetic acid (Milhorat, Thomas and Techner, 1932), glycine (Armstrong and Herbert, 1935), vitamin B_6 (Antopol and Schotland, 1940) adrenaline and pilocarpine (Schäffer, 1949), insulin (Mayerhofer, 1950), resection of the carotid sinus nerve (Meurer, 1950) and inositol (Beckmann, 1951), but none of these methods has proved to be of lasting value. Many other papers have paid tribute to the therapeutic efficacy of wheat germ oil or of vitamin E and its analogues in this group of disorders (Bicknell, 1940; Rabinovitch, Gibson and McEachern, 1951) though many other workers have found these substances to be ineffective (Fitzgerald and McArdle, 1941; Harris, 1941; Doyle and Merritt, 1941; Minot and Frank, 1944). Recent work (Merritt, 1952) has also shown that ACTH and cortisone are of no value.

The trial of treatment in our cases was carried out in view of the persistent reports that a small proportion of patients may improve on vitamin E or wheat-germ therapy. It was felt that our series was sufficiently extensive and the period of treatment sufficiently long to prove or disprove this suggestion. The use of nicotinamide as one form of treatment has no scientific basis, but it was felt that this group, together with the control

group, would serve for comparison with the three groups receiving different forms of wheat germ and vitamin E.

The forms of treatment given to separate groups of cases were purely empirical, being based upon the remedies used with apparent success in the benign childhood cases reported elsewhere (Walton and Nattrass, 1954). They were:

A. Ephynal (Roche)-synthetic α-tocopherol, 50 mg. three times daily.
B. Wheat-germ oil (Crookes)—one capsule (each containing 3 mg. of combined tocopherols) three times daily.
C. Tocopherex (Squibb)—one capsule (each of 3 minims, containing 50 mg. of a mixture of α-, β- and γ-tocopherols in oil) three times daily.
D. Nicotinamide (B.D.H.), 100 mg. three times daily.
E. Inert tablets, one three times daily.

It will be seen that three different forms of vitamin E were tried; pure α-tocopherol was given as one remedy, while mixed natural tocopherols were administered in low dosage to one group and in high dosage to another. These variations were tried in view of the allegations made by certain authors that a substance other than α-tocopherol, but present in natural wheat germ extracts, is the effective principle, and also because others have suggested that high dosage is for some reason ineffective.

Each form of treatment was given to approximately 20 patients; each treatment group was designed so as to contain, as far as possible, equal numbers of cases of the different types of myopathy. Selection of cases was otherwise carried out at random by an independent observer; each patient was given an unmarked bottle containing six months' supply of tablets or capsules, and a letter signifying the treatment given was placed in a sealed envelope in the patient's clinical record. Each patient was seen again at the end of the six months' period of treatment by one of us (J. N. W.); the subjective effect of the therapy as reported by the patient was noted and an objective assessment was made by repeating the measurements, movements and tests of muscular power which had previously been carried out when he or she was in hospital. It must be stressed that at this time the observer was not aware which treatment each patient had received; this was only discovered when the sealed envelope was opened after the clinical assessment had been made. All patients were examined again, save for 5 who died, a further six months after treatment was discontinued, in order to discover whether significant deterioration had occurred.

Results.—The results of treatment in 98 of our cases are given in Table XXI. The patients with myotonia congenita were not included in this trial and one Duchenne type case failed to return for review.

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TABLE XXI.—THE RESULTS OF TREATMENT IN 98 CASES OF MYOPATHY

	Treatment received																								
	Synthetic tocopherol					*Wheat-germ oil*					*Tocopherex*					*Nicotinamide*					*Control*				
Type of myopathy	*Number of cases treated*	*Unchanged*	*Deteriorated*	*Objective improvement*	*Subjective improvement*	*Number of cases treated*	*Unchanged*	*Deteriorated*	*Objective improvement*	*Subjective improvement*	*Number of cases treated*	*Unchanged*	*Deteriorated*	*Objective improvement*	*Subjective improvement*	*Number of cases treated*	*Unchanged*	*Deteriorated*	*Objective improvement*	*Subjective improvement*	*Number of cases treated*	*Unchanged*	*Deteriorated*	*Objective improvement*	*Subjective improvement*
Duchenne type	8	4	2	0	2	10	6	3	0	1	10	6	2	0	2	10	6	2	0	1	9	6	2	0	1
Facioscapulohumeral	3	1	1	0	1	3	1	1	0	1	3	1	1	0	1	3	2	0	0	1	3	2	1	0	0
Limb-girdle	3	1	1	0	1	4	2	2	0	0	3	1	1	0	1	4	3	1	0	0	4	1	2	0	1
Distal	—	—	—	—	—	1	1	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—	1	—	—
Ocular	1	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Dystrophia myotonica	3	1	1	0	1	3	1	2	0	0	3	2	0	0	1	3	2	0	0	1	3	1	1	0	1
Totals	18	7	6	0	5	21	11	8	0	2	19	10	4	0	5	20	13	3	0	3	20	10	7	0	3

As will be observed from Table XXI, none of our patients showed any objective improvement as a result of treatment. Subjective improvement often consisted in a feeling of well-being, though some patients insisted that they were stronger. However, it will be seen that this was true of almost as many cases in the control and nicotinamide groups as in the patients treated with vitamin E and its analogues. Statistical evaluation reveals that there is no significant difference between the results in any of the groups. It therefore seems clear that vitamin E and wheat germ are of no value in the treatment of typical cases of myopathy.

Physical treatment must be mentioned briefly. There is no evidence to show that any of our patients improved as a result of massage, electrical treatment or surgical measures. However, deterioration often occurred when a patient was confined to bed; for this reason it seems important that any individual case should be kept moving and encouraged to walk as much as ever possible. On the other hand, over-exertion is to be avoided as it seems likely that this may speed muscular atrophy. Hence frequent but not violent activity should be advised and all limb joints should be moved regularly both actively and passively through a full range of movements in order to prevent contractures which are a serious cause of disability, particularly in the Duchenne type cases. Nor must psychological management be ignored. All patients who are able to work should be encouraged to do so as long as possible; children should be sent to school and others who are unable to attend should be encouraged with hobbies and tasks to occupy their minds. Many patients with these disorders become depressed and introspective in the late stages; a cheerful and optimistic attitude towards them can do a great deal to alleviate the mental suffering which is as great in these conditions as in any form of slowly progressive incurable disease.

Summary

The results of a clinical survey of 105 personal cases of myopathy are reported, with particular reference to the classification and natural history of this group of disorders.

An analysis of clinical and genetic data has led to the conclusion that the commonly occurring cases of muscular dystrophy should be classified into three broad groups, the Duchenne, facioscapulohumeral and limb-girdle types. In addition to these three principal divisions, other uncommon forms of myopathy occur which are clinically and genetically distinctive and include the distal, ocular, congenital and local forms as well as certain myopathies of endocrine and metabolic origin and others which appear to be related in some way to the collagen-vascular diseases (the menopausal and benign childhood types).

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Our observations upon myotonic cases with and without dystrophic features confirm that, despite differences in clinical presentation and course, they all form part of a single disease process. However, there is still ample evidence to show that from the point of view of natural history this single disease process contains three separate clinical syndromes. We feel therefore that the whole should be termed "the myotonic syndrome," while its component entities should be referred to as the dystrophia myotonica, myotonia congenita and paramyotonia forms.

Using this classification, our series of cases consists of 48 Duchenne type cases, 15 scapulohumeral, 18 limb-girdle, 2 distal and 1 ocular case, and 21 cases of the myotonic syndrome, 15 of the dystrophia myotonica and 6 of the myotonia congenita forms.

The Duchenne type muscular dystrophy is characterized by (*a*) expression usually in the male but rarely in the female; (*b*) onset usually in the first 3 years of life but occasionally as late as in the third decade; (*c*) transmission as a sex-linked recessive character with a high mutation rate; (*d*) symmetrical involvement first of pelvic girdle muscles, spreading to the shoulder girdles within three to five years; (*e*) pseudohypertrophy, particularly of the calf muscles, in about 80 per cent of cases; (*f*) steady and usually rapid progression without periods of apparent arrest, giving inability to walk usually within ten years of the onset but sometimes much later; (*g*) frequent rapid deterioration after periods of bed-rest; (*h*) progressive deformity with muscular contractures and skeletal distortion and atrophy; (*i*) death from inanition or respiratory infection usually in the second decade but sometimes not until middle life.

The characteristic features of *the facioscapulohumeral form* are: (*a*) expression in either male or female; (*b*) variable age of onset at any time from early childhood until late adult life; (*c*) transmission usually as an autosomal dominant gene, occasionally as an autosomal recessive; (*d*) the occurrence of abortive cases; (*e*) involvement, sometimes asymmetrical, of facial and scapulohumeral muscles with, in a considerable proportion of cases, spread within twenty to thirty years to the pelvic girdle; (*f*) muscular pseudohypertrophy is very rare; (*g*) slow insidious progression with periods of prolonged arrest of the disease; (*h*) severe disability does not usually occur and muscular contractures and skeletal changes are slight; (*i*) most patients survive and remain active to a normal age.

The limb-girdle form shows (*a*) expression in either male or female; (*b*) onset usually late in the first or in the second or third decades but sometimes in middle age; (*c*) transmission usually as an autosomal recessive character but occasionally as a dominant; (*d*) primary involvement of

either the shoulder girdle or pelvic girdle muscles with frequent asymmetry of wasting when the upper limbs are first involved; (*e*) spread from the upper to the lower limbs and vice versa, in most cases within twenty years; (*f*) abortive cases are uncommon; (*g*) muscular pseudohypertrophy is uncommon; (*h*) variable rate of progression of the disease, fairly rapid in some, slow in others with sometimes periods of clinical arrest; (*i*) severe disablement with inability to walk is usually seen within twenty to thirty years of the onset; (*j*) muscular contractures are uncommon save in the late stages and skeletal changes are slight; (*k*) death frequently occurs in middle age when the disease begins in the second decade.

In both of our cases of distal myopathy the disease began in the hand and forearm muscles and in those below the knee but later spread proximally; both patients became unable to walk within ten years of the onset. The patient with *ocular myopathy* showed ptosis, symmetrical and severe impairment of ocular movement with weakness of orbicularis oculi, orbicularis oris and of certain limb muscles.

The dystrophia myotonica form of the myotonic syndrome is characterized by (*a*) expression in male or female; (*b*) onset at any age from early childhood to late adult life but usually in the third or fourth decades; (c) transmission via an autosomal dominant gene or possibly by a group of recessive genes; (*d*) onset with myotonia and facial or peripheral weakness; (*e*) myotonia is usually limited to the hand and forearm muscles and tongue but may be generalized; (*f*) weakness of facial muscles, masseter, temporales, sternomastoids and sometimes extrinsic ocular muscles; (*g*) simultaneous symmetrical weakness and wasting of forearm and leg muscles with spread later to proximal muscles; (*h*) muscular hypertrophy occurs rarely in proximal muscles; (*i*) cataract, testicular atrophy, frontal baldness and mental defect or dementia are common in patients and in members of the "dystrophic generation"; (*j*) radiological examination usually reveals that the pituitary fossa is small and the skull vault thick and some cases show cranial hyperostoses; (*k*) the disease is steadily progressive without periods of clinical arrest, leading to severe disability generally within twenty years; (*l*) death usually occurs in middle life. The characteristic features of the *myotonia congenita form* are (*a*) expression in male or female; (*b*) onset usually at birth or shortly afterwards; (*c*) transmission usually as an autosomal dominant factor, sometimes as an autosomal recessive; (*d*) myotonia is the first symptom, is generalized throughout the skeletal musculature and is the sole cause of disability for many years; (*e*) generalized muscular hypertrophy is common; (*f*) dystrophic signs develop in many cases but often not for very many years and even then they remain minimal; (*g*) the disease is generally compatible

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with survival to old age without serious disability. We have no personal experience of *the paramyotonia form,* but it appears to be similar to myotonia congenita, save for the fact that myotonia occurs only on exposure to cold.

Electrocardiograms were abnormal in 12 of the more advanced cases of Duchenne type dystrophy in our series, raising the possibility of cardiac involvement. More severe abnormalities were observed in the tracings from 11 of the cases of dystrophia myotonica. The urine of 89 cases was examined for the presence of ribose; the test was positive in 12 cases and negative in the remainder; since specimens from 2 patients with motor neurone disease also gave a positive reaction the test is clearly of no value in diagnosis.

The results of a trial of treatment in 98 cases are reported; the patients were divided into five groups, selection being made at random save for the fact that each group contained comparable numbers of patients with the various forms of myopathy. A different form of treatment was utilized in each group of cases and every patient was treated for six months. The remedies used were synthetic α-tocopherol, wheat-germ oil, mixed natural tocopherols, nicotinamide and a control substance. Detailed clinical testing of muscular power and certain test movements were carried out in all cases before treatment was begun and were repeated at the end of the course. The observer responsible for making the final clinical assessment was not aware of the type of treatment each patient had received until after the assessment had been made. No case showed objective improvement, and, while a number of patients in each group showed slight subjective improvement, statistical evaluation gave no evidence that any of the remedies utilized had had any significant effect upon the course of the disease. It is concluded that in the present state of knowledge vitamin-E therapy is of no value in the treatment of typical cases of myopathy; patients should be encouraged to move about as much as possible and to take moderate exercise, while frequent active and passive movements of the limb joints should be carried out in order to prevent contractures.

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THE VI LATIN-AMERICAN NEUROSURGICAL CONGRESS

The VI Latin-American Neurosurgical Congress will be held in Montevideo from March 21-24, 1955. The provisional programme includes discussions on brain herniations, pain surgery, dyskinesias and a symposium on the thalamus. Details can be obtained from the Secretary-General, Dr. R. Arana-Iñguez, Convención 1287, Montevideo, Uruguay.

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PHOTOGENIC EPILEPSY: SELF-PRECIPITATED ATTACKS

BY

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THIS communication deals with epilepsy precipitated by flicker induced by the subject.

Search of the literature, including that of sun-worship, failed to reveal any early reference to epilepsy produced by flickering light. In 1927 Gordon Holmes wrote: "Some men subject to epileptiform attacks commencing with visual phenomena owing to gunshot wounds of the occipital region have told me that bright lights, cinema exhibitions and other strong retinal stimuli tend to bring on attacks." Although Holmes discussed true reflex epilepsy provoked by a constant visual stimulus, the above may be the first recorded instance of the effect of flicker, for flicker was characteristic of the early cinema. (The colloquialism "flicks" will be recalled.)

In 1932 Radovici, Misirliou and Gluckman described a case of "reflex epilepsy provoked by optic excitation from rays of sun." For ten years a man of 20 years had suffered from a tic consisting of rhythmical upward movements of the head with tremors of the eyelids when looking towards the sun on bright days. Occasionally this was followed by convulsive crises. This apparently compulsive manifestation occurred after schoolmates frightened him and forced him to look at the sun. In 1934 Catola described a case of "visual sensory epilepsy due to sunlight." Goodkind (1936) described uncontrollable generalized jactitatory movements which occurred a few seconds after the patient's face had been exposed to the sun. This was sometimes followed by a typical major epileptic convulsion. In 1947 Stanley Cobb described 3 cases under the title "Photic driving as a cause of clinical seizures in epileptic patients." One of his patients suffered from attacks as he drove in a car along a road with sunlight slanting between tree trunks. A flickering arc light outside a village store caused temporary blankness of mind in another, and the third had short periods of mental confusion while conducting experiments with a rapidly flickering light in a physics laboratory.

In 1946 Walter, Dovey and Shipton reported that intense flickering light was capable of inducing epileptic discharges in some epileptics. This phenomenon has been the subject of sustained interest in the laboratory of Henri Gastaut (Gastaut and Gastaut, 1949; Gastaut and Hunter, 1950; and Gastaut, 1950 and 1951). Gastaut (1951) found that *grand mal, petit mal* and bilateral myoclonus, or combinations of these, could be produced by intermittent light stimulation. He stated that it was never a question of continuous light, whatever its intensity, but always of a flickering light of rapid frequency. Attacks might be produced by (*a*) the rhythmical standing out of the trees against the sky during a car or a train drive; and (*b*) reflection of sun or waves or snow, producing intermittent and capricious play of the sun. He made one remark pertinent to this paper. Two children "were searching for epileptogenic stimuli to provoke their absences: one of them by passing rapidly his hand with the fingers widespread before his eyes, the other by moving his hand rapidly from right to left in front of a window with coloured glass." The resting electroencephalographic record was usually normal. Light stimulation (with a flash frequency mostly about 15 per second) produced attacks of the clinical types mentioned above, with corresponding electroencephalographic patterns.

Bickford (1949) reported that electrical responses to flicker occurred in a considerable proportion of normal subjects. In 92 per cent of 50 subjects the frequency of flashing, or a multiple or submultiple of it, was reflected in the occipital and parietal records. In 10 per cent slow (delta) frequencies, unrelated to the frequency of flashing, appeared. This was associated with unpleasant feelings of dizziness and disorientation, and in one case a clinical seizure followed. In 14 per cent paroxysmal discharges, unrelated to the flash frequency, occurred synchronously over the whole cerebral cortex.

Bickford, Daly and Keith (1953) reported observations of the convulsive effects of light stimulation in 27 children, some of whom had attacks following exposure to the flickering light encountered in everyday life, as when driving along a tree-lined road when the sun was low. Some patients complained of "difficulty when looking directly at the sun or at reflected light from snowscapes or water. Young children may manifest this by blinking or rolling of the eyes." In 2 cases waving of the hand when facing the sun or a bright light produced enough flickering to induce attacks. One patient had attacks when he looked at cloth of fine texture, a fine copper mesh, and his doctor's tie. The first of these was observed as early as 1947 (Bickford, personal communication). They suggested that three groups exist, "(*a*) a clinically sensitive group in which light of the intensity encountered in daily life is capable of inducing clinical attacks; (*b*) a less sensitive group in which clinical seizures can be induced only under con-

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ditions of high intensity of illumination and rapid flicker which can be produced in the laboratory and, finally, a group (*c*) in which the only evidence of sensitivity is the occurrence of seizure discharge in relation to stimulation by light and unaccompanied by any detectable clinical evidence of seizure."

They found no constant pattern in the electroencephalograms. In three-quarters of the resting records there was diffuse high voltage 3 per second spike-wave discharge. Five patients showed focal sharp wave discharges confined to the occipital regions. There were often rhythmical bursts of high voltage waves related to closing of the eyes. Flickering light produced diffuse spike-wave discharges, in many with multiple spikes and a myoclonic pattern. Flash frequencies between 10 and 20 per second were most effective. A single flash produced attacks in one patient. The type of attack varied; arrest of speech, mental confusion and loss of consciousness, myoclonic jerking, turning of head and eyes and, if the flashing was prolonged, a generalized convulsion might ensue.

Photic excitation has been subjected to intense study in electroencephalographic laboratories, and much knowledge of theoretical importance has emerged, especially in the laboratories of Grey Walter and Gastaut. Since flicker may precipitate diagnostic dysrhythmias in epileptic subjects it is now widely used as a means of "activation" during electroencephalographic recording. Yet clinical descriptions of photogenic epilepsy are few, and self-precipitation of epilepsy has been given little notice except by Bickford. The fascination of symptomatology would seem to justify the recording of the following 7 cases. The informants' words are used throughout the histories, and some repetition has been allowed to convey subtle grades of meaning.

Case Reports

Flicker is produced by interrupting the sun's rays in two ways, either manually, or by blinking.

Group I.—Flicker Produced Manually

The patient interrupts the sun's rays by moving the abducted fingers or the hand across one eye.

Case 1.—The mother of a shy but charming girl of 5 years stated that her daughter made a peculiar movement of her hand across her eyes when she was in the sun. The peculiar look which accompanied the gesture made her mother fear insanity.

When the mother was reassured that this was not the case she gave the following history:

When 2½ years of age, the patient and her brother started to play "a game of looking at the sun and seeing things." The brother later ceased, but the patient continued. Her grandmother used to tell her to brush the hair out of her eyes, and this was thought to be responsible for the habitual hand movement.

Subsequently her mother would see her pause, look up at the sun, and make

one or two passes of the left hand, with separated fingers, in front of the left eye. She would then turn away from the sun. At first only the action was noticed, but twelve months after the onset she seemed to give a nervous little shake when she was doing it. Moreover, " a little something " came over her face which the mother did not like, a sort of blankness. She would pay no attention to her mother when she was doing it, so absorbed did she seem. She frequently stopped during play, or when crossing a road, or when riding her tricycle, remaining motionless until she had made the movement. Once she fell from her tricycle when " doing it."

She makes the movement many times a day when in the sun, and lately she has been doing it inside the house, in front of a sunny window. The sun seems to have a great attraction for her. She deliberately turns to the sun when making the movement, and her parents are able to stop it immediately by walking between the sun and the patient's eyes. Should she be wearing a wide-brimmed hat and sun glasses she will remove them in order to make the movement. Once it occurred in front of an unshaded electric light (which was subsequently removed). When her father tied down her left arm she commenced to wave the right hand in front of the right eye. She is left-handed.

When other children asked her why she did it, she said, " Because I want to." She called it her " silly business " and " got scotty " if anyone mentioned it. When reprimanded, she would sometimes say, " I'm sorry Mummy, I can't help it." Her parents " could get nothing out of her " about it, nor could she be induced to refer to it during examination.

The patient was the younger of two children. The brother (aged 8) was subject to fits of temper, but had no epileptic manifestations. The pregnancy was normal, and labour, at full term, lasted for seven hours and terminated without interference. The baby's condition after birth was good, and she developed normally. She was a

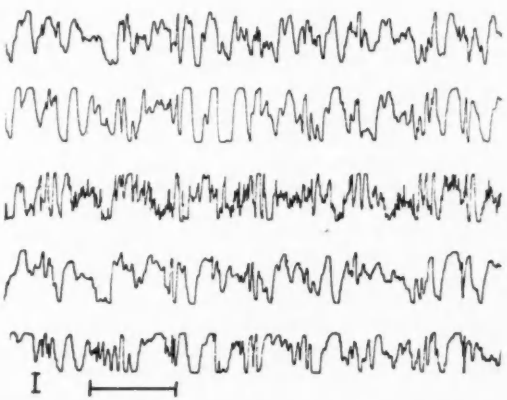

FIG. 1 (*Case* 1).—Continuous irregular high voltage slow and fast waves provoked by photic stimulation. Rate of flash, 12 per second. The patient was able to answer questions throughout. In all figures the recording is bipolar, from para-sagittal pairs of electrodes, the tracings from above-below representing 1, right anterior frontal—right posterior frontal, or rate of flash; 2, right posterior frontal—right parietal; 3, right parietal—right occipital; 4, 5 and 6, similar pairing on the left side. Deflections of 60 microvolts and time intervals of 1 second are indicated on the records.

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nervy child, but had no convulsions. She had a slight strabismus, but this disappeared. She was intelligent, but did not mix well with other children.

No abnormality was found on physical examination.

Electroencephalogram.—At rest 9–10 per second activity of moderate voltage predominated in the occipital region, with a considerable number of random 5 per second waves which increased in frequency during overbreathing.

When she was placed in sunlight on two occasions no hand movement occurred spontaneously, nor could she be induced to make the movement. Movement of the examiner's fingers between the sun and her eyes produced irregular outbursts of high voltage 3–4 per second waves with intervening spikes.

When the eyes were exposed to flickering light of high intensity, the occipital and parietal discharges tended to synchronize with flash rates between 4 and 9 per second. High voltage spikes and 3–4 per second waves occurred sporadically when the flashes occurred from 6–9 times a second. Between 15 and 20 flashes per second the record was continuously abnormal with very irregular high voltage waves between 15 and 2 per second. This dysrhythmia commenced shortly after the flash commenced, and ceased within 2 seconds after it stopped.

A second record was made after the patient had been treated with ·3 gramme troxidone three times a day for some months, and ·6 gramme three times a day for two days before recording. Very little difference was noted in the record. The patient was able to answer questions accurately throughout abnormal outbursts of three minutes' duration (fig. 1). She was slow in answering the first question of each group, giving the impression of having to be awakened on each occasion. From time to time myoclonic jerking of the neck and arms occurred, usually corresponding with an increased number of spikes. The abnormality was reduced by covering one or other eye and it ceased when the light was more than 36 in. from the eyes. She was not distressed during recording and seemed unaware of abnormality.

Progress.—The number of attacks has been slightly less during treatment with troxidone. Addition of phenobarbital, phemitone and phenytoin sodium served no useful purpose. She has been asked to control the movement, but without success, possibly because she is too young to co-operate. "Mysoline" failed to reduce the symptom.

Case 2.—An intelligent schoolgirl, 12 years of age, was described by her mother as having "a funny little mannerism about the eyes." This was ascribed to eye-exercises prescribed years before for a slight squint, in which she gazed at her own hand as it moved from side to side in front of her eyes.

Her mother stated that eighteen months ago, when in the sun, she was noticed to move the right hand in front of the right eye, brushing the fingers along the forehead. At first she did this when she was tired or excited, but later it became very frequent. She would appear vague and confused while "doing her habit," and was liable to bump into objects in her way when walking.

Six months after the onset she was found sitting on the edge of a gutter moving her hand in the manner described and repeating "I don't know where I am." Her mother carried her inside, where she fell asleep. A few months later, while playing croquet, and "making her movement," she fell flat on her face. When her mother turned her over she was quite limp and the left side of her face twitched for about two minutes. She was put to bed, and then slept until the next morning. On another occasion her mother found her "doing it," leaning against a wall with her eyes looking a little peculiar. Her mother knocked her hand down and she came to immediately. On another occasion the patient herself reported that she had felt peculiar while sitting on the side of a swimming pool. Remembering her mother's injunction to stop the movement she chose to put her head down between her knees. Her eyes looked a bit groggy when she came home. A month ago, while on a holiday, she was holding a dog on a leash in the sunshine. She started "doing

her habit," the dog escaped and she collapsed to the ground, muttering "I'll hold him, I'll hold him."

She seemed impelled to make the movement every time she went into sunshine, and never has attacks away from sunlight. She has been seen to make the movement when crossing a road. She adores the sun, and is always going to windows, there to make the movement. Her mother believes that she can prevent it by concentrating. Whenever her father sees her doing it he shouts at her, and she stops immediately. Her mother's quieter voice, however, fails and she has to knock the hand down.

The patient herself gave the following account of her symptom: She faints after "doing her habit" in the sun—she supposes that the sun makes her feel fuzzy. Sometimes when she is very excited she does it a terrible lot, but does not faint then. She will walk over to a patch of sunlight in her room and do it there. In the afternoon she goes to the other side of the house to do it—she cannot say why she seeks the sun—she just goes there. She knows when she is going to faint, and if she is not too muddly she knows she should do something to stop it. She can stop her habit when her father tells her to, but when she is alone she does not want to stop it. She thinks it might give her a bit of satisfaction—a feeling that is difficult to describe—a feeling between satisfaction and not wanting to do it, something like satisfaction but something else which she cannot explain. She likes the sun so much. Sometimes she would go into a little room and do it hard a number of times, and then would leave the room and very firmly shut the door. She thinks that if she were cross and grumpy her habit might give her some relief. She did it once with a baseball glove but it didn't feel very nice and she stopped it.

Her mother gave the following account of her early life: The pregnancy was apparently normal. Labour, at full term, lasted about eight hours. Delivery was non-instrumental. The baby's condition was good after birth, although her forehead was blue in colour. As an infant, she was prone to hold her breath and twice she became cyanosed. She had no infantile convulsions.

There is no known family history of epilepsy.

No abnormality was found on detailed neurological or general examination.

Electroencephalogram.—The resting occipital record consisted chiefly of 9–10 cycles per second activity, with a number of random 5 per second waves in the frontal records. During overbreathing some irregular slow waves (4–5 cycles per second) of higher voltage emerged in all records, becoming more evident as hyperventilation continued, and subsiding slowly after its termination.

The patient was then placed in the sun with electrodes applied. She was requested to relax and not to prevent her habit should it occur. After an interval she began to glance at the sun and to wave her hand rhythmically in front of her eyes. By means of a rotatory movement of the forearm she moved her abducted fingers across her left eye, so that the light was interrupted by each finger in turn. In this way about 15 fluctuations of light were produced in a second. An abstracted look appeared in her eyes. From the general background of muscular artefact due to movement, small groups of slow waves (3 cycles per second) and spikes emerged from time to time, sometimes more evident on the right side than on the left. When she was "doing it properly" (i.e. producing "the feeling") continuous high voltage slow waves and spikes were seen.

Photic stimulation: At 7 flashes per second, a marked tendency to synchronization of flash and 7 per second cerebral waves occurred. At 10 flashes per second high voltage 3–5 per second waves occurred irregularly with many intervening spikes. This continued until she said, in alarm, that she was feeling as if she was going to faint, when the light was switched off and the normal rhythm quickly returned. All rates of flash between 10 and 32 per second provoked similar outbursts (fig. 2A). The abnormal response was slower in appearance when the eyes were open than when shut. Closing both eyes was followed immediately by the high voltage response

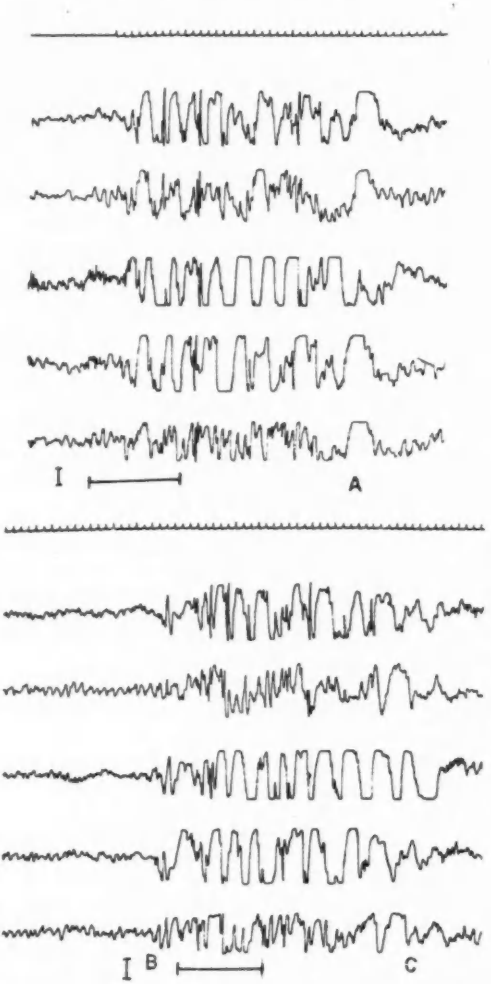

FIG. 2 (*Case* 2).—A, Response to 11 flashes per second, ceasing when the left eye was covered (at A). B, The record commences with eyes open. B eyes were closed, and at C the right eye was covered.

(fig. 2B). Covering one or other eye whether the eyes were open or shut (fig. 2) caused a return to normal rhythm.

It was found that the abnormal response ceased when the light was 40 in. from the closed eyes and 18 in. from the open eyes.

Progress.—Troxidone was prescribed, and the part played by the movement explained to her in the hope of impressing upon her mind the need for restraint. She was asked to avoid seeking the sun. When taking ·9 gramme of troxidone per day she experienced severe and uncomfortable photophobia for about five minutes when going into the open. During this period she could hardly see, and she did not

"do her habit." However, she did it when the glare effect passed, although less frequently than before. The troxidone was reduced to ·6 gramme and the glare phenomenon disappeared. In the early days of treatment she had one attack in which she became cyanosed, and another in which the left side of the face twitched. No such attack has occurred for twenty months. Her mother stated that she has taken the control into her own hands and is succeeding marvellously. She does not now dash into the sun to do it, and only once when very upset was she found outside doing her habit. She was very apologetic about it afterwards. The patient herself said that she often felt tempted to do it, but could succeed in controlling it, unless she was very bad-tempered. (She says that she now knows when she is doing it. She finds herself beginning to do it, and then pulls her hand away. She still has the tendency to do it when she gets very cross. However, she says, there are lots of other ways of getting cross. It used to be hard to stop it, but it is now easier.) Prior to going to the beach she agreed to take dark glasses provided with side pieces, although previously her mother had never been able to induce her to wear glasses.

However, her mother added that as she leaves home to go to school she is often seen to look at the sun without making any movement of her hands. Her mother says that she throws her head back to the sun, as if it hits her when she goes out.

Twenty-two months after she was first seen she reported that she does not "do her habit" any more. She prevents it by stiffening her arms. It was difficult at first. Sometimes even now she feels that she wants to make just one pass, and then she stops it. However, she now seems to look at the sun and then her eyelids flicker, but she does not feel faint. She has no idea why she does it. She finds herself doing it, without any conscious thought, and often does not realize she is doing it. She thinks it gives her a better feeling than her old habit. She added that she always knows where the sun is. Once she was doing it while a snapshot was taken, and her appearance shocked her and made her want to stop. She recognizes no feeling of compulsion, nor any feeling of tension if she tries to stop it, but as yet her attempts have not been as successful as with her hand habit. During the winter, however, she did not do it, but now that the sun has come out it is harder.

Case 3.—A housewife of 41 years stated that she had influenza in 1919. She cannot remember any details of the illness, but she believes that she was very ill. Her mother had the same infection, and died subsequently of heart failure. Subsequently the patient had "blocks in the brain, accompanied by a hand waving." (At that time the world-wide epidemic of influenza had reached Australia. Whether she had encephalitis, or whether encephalitis had any influence upon subsequent developments is problematical. However, this point may come to mind when the thalamic theory is being discussed.)

Her right hand, with spread fingers, passed between her right eye and the sun or glare. At the moment of doing it she was not aware of it, but she was aware of having done it instantly afterwards. This continued, sometimes many times a day, for more than thirty years. Sometimes it happened during speech and then her mind would cut off, prompting being necessary before she could go on. She felt embarrassed to find people looking at her curiously. In later years the attacks were usually very brief, and accompanied by a single wave of the hand; sometimes when she was very tired or emotionally upset several passes occurred and the attacks were then of longer duration. After marriage, her husband used to try to stop it by holding her arm and this would give her a frightful shock, like waking a sleep walker. The sun, she stated, acted like a magnet and made her look at it. When inside, glare caused by clouds shining through a window compelled her to turn towards the window—like a moth to a candle. The light seemed to go right through into her brain. This, she believed, made her put her hand up to break the light and protect her brain. She felt keyed up whenever she was in the sun and the tendency "to do it" nearly

drove her silly. If she concentrated hard it did not occur, but when she was tired she could not concentrate. She was a tennis player of championship class, and found that it did not happen during play, but only between rallies. It happened more frequently when playing golf, and on her bad days she was often embarrassed by the questioning stares of other players. She found that wearing polaroid glasses reduced the glare and attacks were less frequent.

On two occasions during the last six months she lost consciousness. Each time she was making a bed, under great emotional strain and feeling very tired, having had little sleep and much alcohol. She experienced a remote sort of feeling, a feeling of exhaustion and faintness more than anything else. She was told that her eyes turned up, her jaw moved in a grinding fashion and her colour became blue. She thinks that there was no hand movement prior to these attacks, but she cannot be certain.

She has always had a frightful battle against the condition which occurred whenever she was in bright light. It occurred more frequently in the mornings when she was tired or tense. She thought the hand movement to be an integral part of the attack, but not the precipitating factor. She lost confidence in herself, never knowing when an attack would catch her in front of people. Pain in the back and domestic tension added to her unhappiness.

As in the other patients, physical examination disclosed no abnormality.

Electroencephalographic recording was carried out on three occasions. The resting record was a normal one. Well-defined alpha rhythm, of somewhat variable voltage, predominated in the occipital region. It was normally suppressed by visual stimulation. No spontaneous attack occurred for some time when she sat in continuously pleasantly warm sunshine. An attack was precipitated by flicker produced by the examiner's hand. Flicker at the rate of approximately 15 per second produced a short series of low-voltage 2-per-second waves, most clearly defined in the frontal leads, with superimposed spikes. These increased in frequency and amplitude until an outburst of high-voltage 3-per-second activity occurred in all leads, with intervening high-voltage spikes. These outbursts lasted about 1¾ to 2½ seconds. In

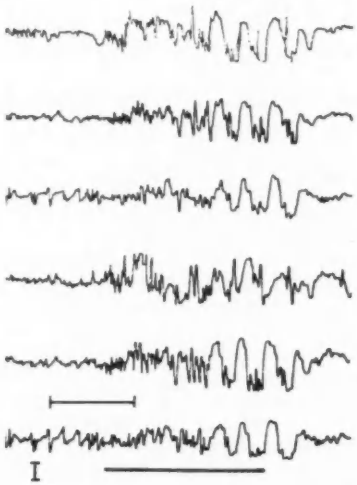

FIG. 3 (*Case 3*).—A manually self-induced attack, recorded in sunlight. The horizontal line records the duration of the movement of the patient's hand.

each she closed her eyes and looked downwards from the sun, apparently thus terminating the attack. Sometimes these attacks were associated with an upward movement of her arm. Subsequently she was asked to imitate her usual spontaneous movement, and similar discharges occurred. When such attacks were produced in rapid succession, she had a peculiar unpleasant feeling of faintness which persisted between the outbursts. Soon afterwards two self-induced attacks occurred (fig. 3). On one occasion, after some twenty attacks were so produced, a brief outburst of high-voltage slow wave-and-spike activity occurred spontaneously, without flicker. The electrical discharge was similar under all circumstances.

Treatment.—Troxidone produced photophobia but did not lessen the attacks. Malidone did not produce photophobia, but both drugs produced a feeling of depression which made continuance very unpleasant. Phenytoin sodium failed to modify the attacks. The addition of phenobarbital or phemitone made her feel more tired and she was convinced that the tendency was worse. Because she felt worse when tired, dextroamphetamine sulphate was tried, and she has found this more helpful that the usual epileptic medicaments. She attained only slight control over the movement.

Case 4.—The mother of a 12-year-old boy states that he commenced to have attacks three years before. In some he appeared dazed for a few seconds, and in others he collapsed in a dead faint, and once a generalized convulsion occurred. She remarked that he had been bad with his hand all day before the convulsion and, on enquiry, she said that all attacks, as far as she could remember, had occurred when out of doors.

She then clarified these points in the following manner. He has a habit of waving his hand in front of his eyes when in the sunshine. When she first observed this, two-and-a-half years ago, she asked him what he was doing and he replied that he had spots in front of his eyes. Sometimes he walked up and down the garden path some thirty times making the movement; turning his head towards the sun when retreating from it. It occurred while he was playing sports. On one occasion he caught a football and, before kicking, turned towards the sun to make the movement. He often walked towards a sunny window to do it. On one occasion it was observed while in a fog, at all other times the sun has been out. Children at school followed him about imitating his movement and making fun of him. Later a patch of short hair was noticed in his right frontal region, so evident that his mother accused him of cutting it. He often returned home from school with a black patch on his forehead, and the thenar side of the back of his hand dirty. At first he would stop when told to do so, but later this was ineffective. He made up to thirty rapid passes with his right hand in front of the right eye, violently brushing the right side of his forehead.

On some days he seemed very confused and forgetful. He was one year behind his age group at school. His teacher said that he had brains, but something seemed to pass over his mind from time to time, and he had difficulty in concentrating. During the previous twelve months he had been wetting the bed at night.

The patient was an intelligent and co-operative boy. In response to questioning he stated, "When running about I sometimes get a dizzy head. Sometimes I go out to it and sometimes I don't. Waving the hand might have something to do with it. When the sun is out, or if I am near a window, I am tempted to wag the hand. I try not to, but there is a kind of nitch in my mind that makes me do it. I try to think of something to do to keep my mind off it. Sometimes I remember after taking my hand up once, and try to stop it. At other times it just goes on. If it goes on for too long I can't stop and this might lead to a turn. I don't feel uncomfortable if I stop it. It isn't pleasant to do it, but I just can't help it. I suppose that I have got into the habit of doing it, and cannot stop. I am so used to doing it that I cannot think whether I want to do it or not. When I look at the sun, it seems to pierce the

right eye and touch a nerve or something, and I feel as if I want to do it. My mind goes blank for a second or so after longer waves. I'll try to do it to show you what it is like," and then he walked to a window through which the sun was shining brightly and beat his semi-closed right hand up and down in front of the right eye and forehead. His eyes shut with the first beat and were occasionally opened and shut very rapidly two or three times during the twelve beats which occurred. The movement stopped abruptly and the series was repeated three times with very brief intervals between. He remained standing throughout, with a rather tense facial

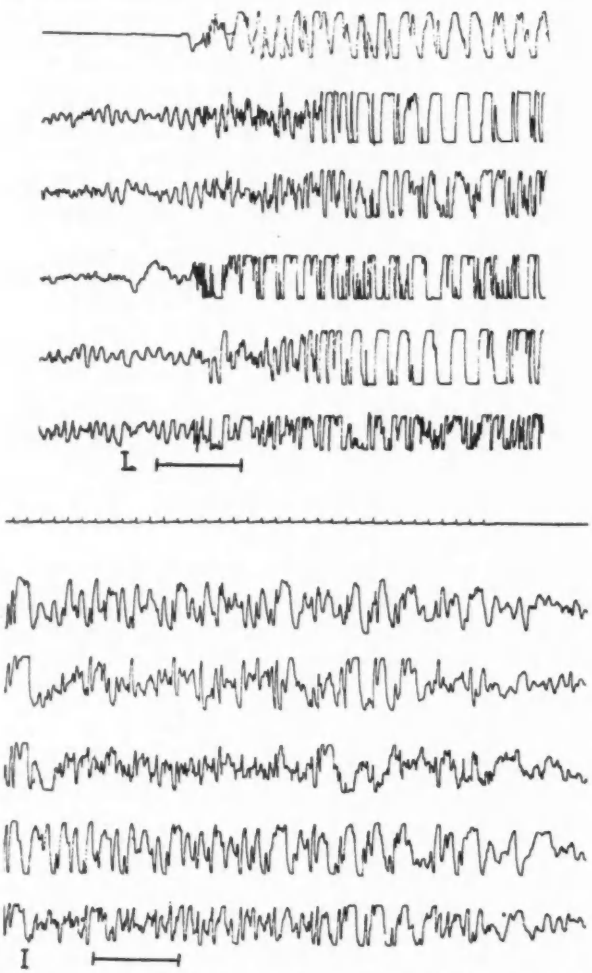

FIG. 4 (*Case* 4).—A, Dysrhythmia provoked by violent beating of hand across the right eye. The upper tracing records movement of forearm. B, Cessation of dysrhythmia when flash ceased after 80 seconds of continuous abnormality. The patient counted up to 100, slowing a little at the end.

expression, and stated that he thought that the attack occurred spontaneously in spite of his intention to imitate.

After the winter months he said that he hardly ever did it in winter, but with the coming of summer he was doing it much more frequently. In spite of attempted observation he was no clearer why he did it than before. He remarked that in the mornings he walks to a window, as if he has to go there, to make the movement.

There was no family history of epilepsy, nor any abnormality of pregnancy, labour and early life.

Electroencephalogram.—When resting, rhythmical very well-defined 7 cycles per second activity was characteristic of the occipital, parietal and temporal regions. Very occasionally low voltage 4 per second compound waves occurred. Overbreathing produced a marked increase in slow frequencies, sometimes with associated fast sharp waves.

An electrical circuit through the forearm and one channel of the electroencephalograph was arranged to record movements of the forearm. The forearm crossed the right eye twice during a single recorded fluctuation. When he was exposed to direct sunlight, movement of the arm commenced, causing eight interruptions of light per second, and also immediately spikes and slow waves appeared in the electroencephalogram (fig. 4A). Many of the slow waves had half the frequency of the interruptions. The movement of the arm tended to accelerate, producing up to fifteen interruptions per second. The disturbance continued until the blind was pulled down or the movement ceased spontaneously. Some 30 seconds after the onset the patient would cease to respond to questioning. There was no obvious change in the record corresponding to this. Attacks on this occasion lasted up to one minute, and after a number the patient was confused and unwilling to move for some minutes.

Photic stimulation.—Six flashes per second produced high-voltage 6 cycles per second waves, with well-marked spikes in some leads, finally breaking into irregular 3–4 per second waves with high-voltage spikes. During 80 seconds of abnormal discharge he counted to 100, although slowing up a little towards the end (fig. 4B). At a flash frequency of 7 there were more high voltage waves (slow waves around 5 per second and rapid around 18), and during these outbursts the patient quickly ceased to count and did not reply to questioning. After the attack he was sometimes able to remember what had been asked, sometimes not. Flash frequencies between 7 and 10 per second were most effective, but abnormal discharges were provoked at all speeds up to 22 per second. Myoclonic twitching of neck musculature was observed to coincide with collections of high-voltage fast waves.

The dysrythmia was provoked whether the eyes were open or closed, but more easily when closed. Closing the eyes tended to provoke outbursts almost immediately and covering one or other eye resulted in cessation of the outbursts. Reduction of illumination eventually resulted in cessation of responses. When an attempt was made to stimulate homonymous hemianopic fields, greater illumination was necessary to provoke attacks, but the abnormal discharge commenced synchronously in the two cerebral hemispheres.

Treatment has had no effect upon this patient. An attempt is being made to induce him to avoid walking to windows and to prevent the hand movement.

Group II.—Flicker Produced by Blinking

The flicker is produced by the action of the eyelids.

Case 5.—A man of 18 years stated that, during the last eight years, he has been unable to stop himself looking at the sun. The sun seems to attract him, and he blinks because it is so bright. Every time, and as soon as he goes outside on a sunny day he looks up at the sun and blinks. He feels dazed and is not fully

conscious for a second, then his mind comes back again. He stops if he is speaking, but is able to pick up the trend immediately. He adds that when he goes into the sun, thinking of anything, the light blinds him and puts him off his thought for a moment. He has been aware that his eyes were closed for a brief interval when crossing a road, but he knows where he is in his memory, and can walk with his eyes shut. Once he was knocked down, quite unexpectedly, by a motor-car.

His mother gave no evidence suggesting injury during birth. Pregnancy was apparently normal, as also was the baby's condition after birth. He was said to have been concussed twice as the result of falls in infancy, being found unconscious on the ground.

He had suffered from attacks of *petit mal* from a very early age, and had one convulsive attack when he was 10 years of age. On a few other occasions he had fallen in attacks, but as he was away from home, no description was available. However, it seems probable that these attacks were of major epilepsy. There was no family history of epilepsy.

Electroencephalogram.—The characteristics of the record were the frequent appearance of 7 per second waves in rhythmical sequence during the resting period. During overbreathing these increased in amplitude and occasionally 2–3 per second waves emerged in the frontal regions. No effect was noticed when his eyes were suddenly exposed to sunlight, nor when he was asked to suddenly look at the sun. However, slow flicker produced by a card moving between the patient's eyes and the sun produced 3 per second high voltage waves in the parietal and occipital leads, usually spreading into the frontal regions, and occurring in more or less rhythmical sequence with spikes in varying relationship.

When flicker was produced over his closed eyelids he invariably opened them, although asserting that he was not aware of having opened them. When the flicker (at a rate of about 3–5 per second) was maintained for any length of time he had the feeling that he would lose consciousness.

Photic stimulation was carried out when he was taking troxidone and phenytoin sodium and after a summer in England, during which he thinks that there was less tendency to look at the sun. It produced irregular slow waves of moderate voltage, the most effective frequencies being about 4, 11 and 20–22 flashes per second. The characteristic slow wave and spike activity of the earlier record was absent, possibly because he was being treated with troxidone, or more probably because the flash did not equal the sun in brilliance. The attacks were more readily provoked when the eyes were open than when shut, and if an attack occurred when the eyes were shut he opened them and blinked, although he was unaware of this. If the eyelids were held closed manually, contractions of the orbicularis oculi were palpable. At low frequencies the attacks tended to cease spontaneously, but at 20–22 flashes the abnormality continued until the flashing stopped, or one or both eyes was covered. When the abnormality was continuously present, he was able to reply to questions and to do small sums, although slower than during normal periods and sometimes inaccurately. The inaccuracy was greater at the end of the longer periods of dysrhythmia.

Treatment.—Hydantoin sodium and phenobarbital appeared to suppress the major attacks. Troxidone, malidone and phemitone did not materially reduce the tendency to look at the sun.

Case 6.—A mentally defective girl, an inmate of a mental hospital, was noticed to be suffering from *petit mal* when 16 years of age. She was treated with troxidone and phenobarbital. When 17, during the last two months, it was noticed that she had attacks only when in the sunshine. If she looked at the sun she had repeated small attacks in which she blinked, jerked her head and, if standing, tended to sway backwards. During this time, on two occasions on very sunny days, frequent minor attacks preceded major convulsive attacks.

Electroencephalogram.—The resting record was a very irregular one. Alpha rhythm was obvious in all areas, but random low voltage waves between 3 and 6 cycles per second occurred at all areas. From time to time spontaneous slow waves and spike discharges occurred. There was no change in the patient's appearance during the brief attacks. However, in those which exceeded 6 seconds in duration, the patient became tense and slightly cyanosed. She swallowed and protruded her tongue slightly.

When in sunlight she sometimes looked directly at the sun, and blinked her eyelids rapidly (about 4 blinks per second). After some four to seven seconds the blinking ceased, and after a brief period of lower voltage activity slow waves (between 3 and 6 per second) appeared, with an almost equal number of high-voltage fast waves (fig. 5). She appeared to be unconscious during the bout illustrated,

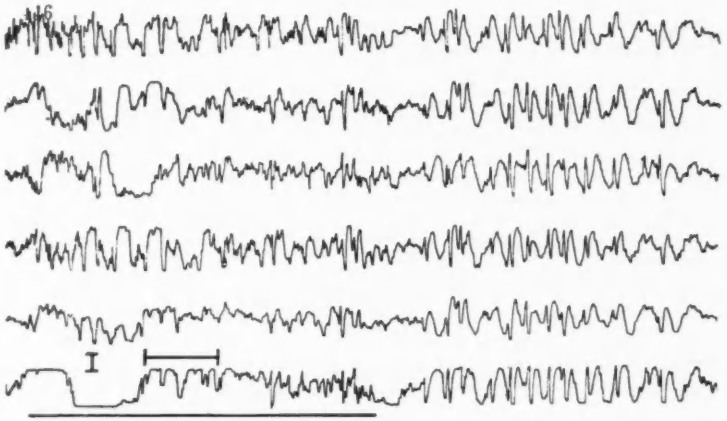

FIG. 5 (*Case* 6).—Myoclonic attack following blinking in sunlight. Duration of blinking indicated.

and irregular twitching of the left arm occurred. Sometimes she would look at the sun when requested, but soon refused to do so. Similar attacks occurred when her head was forcibly turned so that she faced the sun, even when her eyes were closed.

Treatment with troxidone, paradione and phenobarbital has not altered the frequency of attacks.

Case 7.—A woman of 30 years was brought into hospital with abraded nose and forehead, her face being covered with blood. Her mother stated that she had found her lying face down, unconscious, in the garden. She had had two previous such attacks when she was 9 and 18 years of age, but the early stages had not been seen. Each attack had occurred out of doors and she was found lying face downwards, pale, cold and unconscious. At other times she blinked in the sun in a curious way and her expression seemed dulled. When she was younger she moved her hand in front of her eyes when in the sun, but this had not been noticed for many years.

The patient herself said that these attacks only occurred when she was out in the sun and that she knew it was the sun that did it. She felt that she must look at the sun which made her eyes blink, and meanwhile she felt peculiar. If she continued for a long period, a prolonged attack of unconsciousness tended to occur. She could stop the blinking if she wished. When asked why she did not always

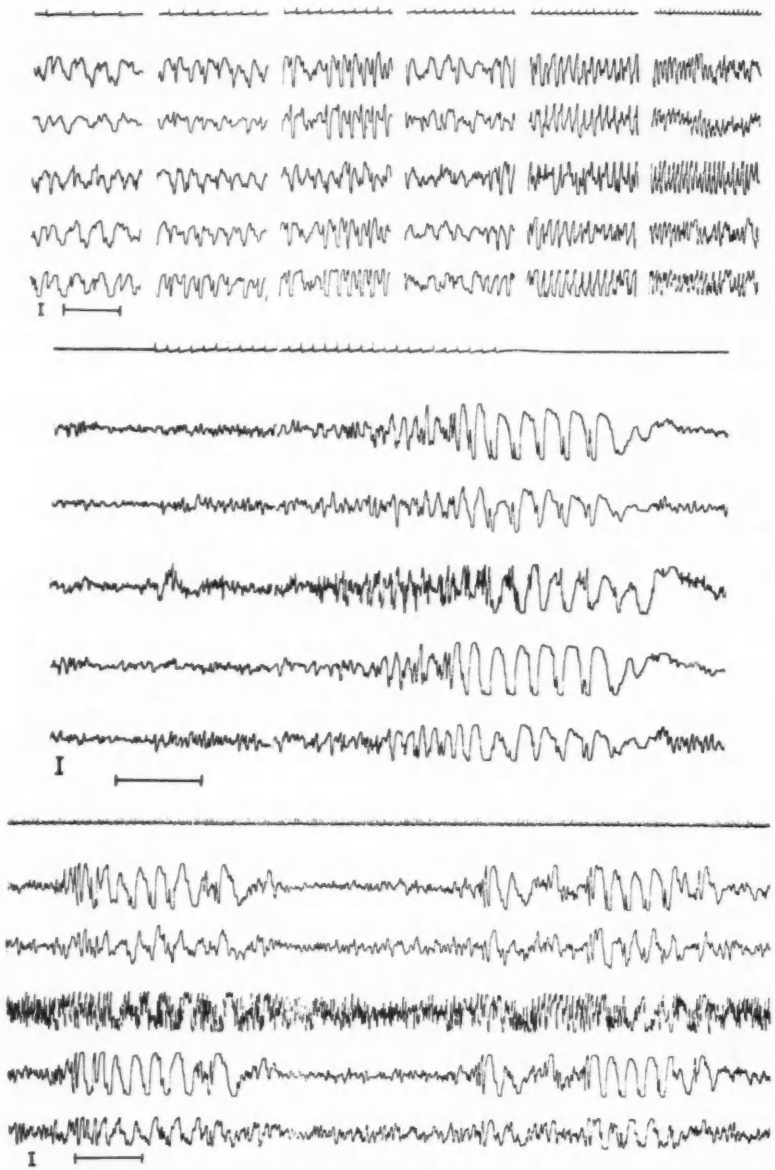

FIG. 6 (*Case* 7).—Photic stimulation of a "blinker"; A, "driving" in response to flashing between 2 and 13 per second; B, response to 7 flashes per second; C, two of a long series of self-limiting attacks precipitated by rapid flicker (30 per second).

stop it, she replied that she did not know; and then added that sometimes when she was a bit upset or excited she hadn't the same control over herself. The attacks never occurred when other people were about, and in order to prevent the bad attacks she avoided spending long periods in the sunshine, e.g. she refused to spend a day on the beach. When asked if any sense of satisfaction accompanied the blinking she replied that " the sun seems to do something to make me look at it—I don't know—it doesn't give me any pleasure. I can't help it in one way, but when I think to stop it I stop. I don't go out and sit in the sun. I get no warning of attacks, but I blink for some time before a bad attack comes on."

On a subsequent occasion (after marriage) she stated that she had an attack at a football match, a game which interests her very much. She was sitting in the open with the sun over her left shoulder. When she became very excited she turned her head to the sun and blinked. Eventually, after she had done this a number of times she had another major convulsion.

Her mother stated that pregnancy, delivery and the neonatal condition were normal. There was no history of epilepsy in the family.

Electroencephalogram.—When seated in the sun and connected to the instrument no deviation from normal behaviour occurred. When asked if she could imitate the movement of her arm which occurred previously, she, very sheepishly, made a movement of the hand very similar to that made by the previously described patients. She was emotionally upset by attempts at provoking attacks by flicker. Her psychological attitude was one of wishing to forget all about the matter, mixed with fear that an attack might be provoked. The record was a normal one. After marriage she was much more equable and, indeed, quite charming. She was prepared to discuss the matter fully, eagerly sought help and submitted readily to photic stimulation.

The initial part of the record showed a remarkable tendency to synchronization of flashes between 2 and 13 per second and the response, so marked that the word " driving " seems apposite (fig. 6A). Between 5 and 35 flashes per second outbursts of spike and 3 per second high-voltage slow waves occurred 1 to 3 seconds after the flashing started (fig. 6B). These subsided after 2 to 4 seconds even when the flashing continued, and recurred at intervals varying between 3 to 8 seconds (fig. 6C). She was not aware of the dysrhythmia and was able to answer questions. The brevity of attacks allowed only for such questions as " Single name . " or " Married name ? " which she answered correctly while the typical wave and spike activity continued.

The discharges were less readily provoked when her eyes were open.

Mode of Production of Attacks

The easiest way to influence the electrical discharge from the cortex is by opening and shutting the eyes. The responses have been studied since the early days of electroencephalography. Later the effect of intermittent light stimulation was tried and was found to provoke clinical seizures in some subjects.

The synchronous onset in symmetrical areas, in frontal as well as in occipital regions, seemed to imply a deep central origin for the cortical dysrhythmia, an origin which was suggested for *petit mal* by Jasper and his colleagues. Indeed, Lewy and Gammon (1940), Morison and Dempsey (1942 and 1943) and Jasper and Fortuyn (1947) recorded this type of response when stimulating the intralaminar portion of the thalamus in

animals. Denis Williams (1953) has recorded human *petit mal* discharges and has shown that the 3 per second rhythm commences in the thalamus and reaches the cortex from there, while the fast spikes originate deep in the cortex.

The response to flicker has been studied by Grey Walter and his associates, by Gastaut and by Bickford. Walter and his associates (1946, 1947, 1949 and 1950) analysed the effect of intermittent photic stimulation during electroencephalographic recording. They considered that flashes of bright light repeated at certain frequencies tended to augment similar existing frequencies and their harmonics, enlisting neighbouring frequencies into the augmented waves. This augmentation of frequencies already present might facilitate explosive epileptic discharges in predisposed patients.

Gastaut and Hunter (1950) showed that a single photic stimulus to the eyes of a normal animal produced a response in the lateral geniculate body and in the primary and secondary visual cortices. The discharges might comprise one, or all three, of the following components:

(i) a rapid triphasic wave;
(ii) a repetitive wave of alpha frequency;
(iii) a slow repetitive wave of theta frequency.

Intermittent photic stimulation at an appropriate frequency caused repetition of the abnormal response which assumed the typical form of the spontaneous discharge of idiopathic epilepsy, i.e. the spike and wave complex. Gastaut (1950) indicated that intravenous metrazol augmented all three components of the response, particularly (iii). Metrazol facilitated the photic response. He showed that the response occurred first in the thalamus, and then irradiated to the cortex. He suggested that there was a thalamic short-circuiting of electrical responses normally carried by the optic pathways. Light impulses were assumed to pass to the pace-making thalamic mechanisms (as well as to the occipital cortex and colliculi), and there provoke an irradiation of abnormal synchronized excitation to the cortex on each side. Metrazol (or light alone in some patients) might open up such connexions in the thalamus which are normally impermeable. In some patients, perhaps due to some thalamic abnormality, a similar dysrhythmia may be provoked apparently spontaneously, thus producing *petit mal*, or myoclonic epilepsy.

Discussion

The condition described is marked by the provocation of cerebral dysrhythmia by action of voluntary muscles.

Brief induced attacks may produce no alteration in the patient's appear-

ance while recumbent during recording, and the patient may apparently be unaware of short attacks. He may be able to reply to questions while the machine shows grossly abnormal electrical discharge. The perceivable attacks vary: *absences,* or *petit mal,* or myoclonic jerking may occur. If stimulation were prolonged generalized twitching might ensue.

State of consciousness.—It is striking that consciousness is retained, although doubtless somewhat impaired, in the presence of such gross electrical abnormality. Duration and, to a lesser degree, repetition of the response caused a progressive impairment of consciousness, although there was no detectable change in the record, unless myoclonus or convulsion occurred. It has been suggested recently that the seat of consciousness lies in the intralaminar portion of the thalamus, which has been called the highest centre. Apart from any other considerations the observations recorded are more consistent with the hypothesis that consciousness is a function of highly-specialized perceptive cortical cells which suffer progressive impairment of function related to the duration of the abnormal discharge, rather than a property of cells whose function it is to control cortical rhythm. The latter may affect consciousness, being in turn perhaps influenced from elsewhere, but they are not the seat of conscious perception. Thus consciousness may be progressively "taken to pieces," following Hughlings Jackson's general rule for dissolution in the nervous system.

The nature of the movement.—The movement might be regarded as a habit spasm or tic. Certainly the movement is particularly likely to occur when the patient is emotionally tense and it would seem that it leads to a feeling of satisfaction. It differs from most tics in that it has a constant form and occurs only in sunlight. More important still, it has a measurable and widespread effect on the cerebral neurones. Further, the patient does not admit to a feeling of compulsion, nor to psychological discomfort if he inhibits the movement, nor to relief by its occurrence. Close questioning usually elicits the puzzled response that he does not know why he does it. It tends to be less marked when the mind is occupied, but may become rife during excitement.

It seems simplest to suggest that a subject sensitive to intermittent light stimulation has found by chance a method of producing attacks. Why he should choose to produce attacks is obscure. It may be that it gives him some satisfaction, and eventually becomes habitual. In addition, it will be recalled that some epileptics feel unwell, irritable and tense before a major attack and better after it. Perhaps the stimulation of the thalamus suggested as a basis by Gastaut is of importance. If some subjects go too

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far, the result is psychologically, and perhaps physically, distressing to the patient. One became terrified when she felt that she was going to faint.

Frequency.—The recognition of 7 such cases in a period of some twelve months suggests that the condition is not an uncommon one. After a meeting at which the clinical picture was described, the writer was told of 3 cases which had immediately fallen into proper perspective. One was the mother of a medical practitioner. Whenever she went into the sunlight her head went back and she blinked. A fleeting blankness of expression was recognizable. In addition, she had suffered from three major attacks, twenty, seventeen and two years ago. These occurred after periods of overwork and psychological stress, such as the disturbance which changing houses causes to a meticulous personality. In addition, after typing notes of these patients, my secretary observed a cricketer wave his hand between his eyes and the sun and then fall unconscious! Three medical practitioners spoke of the peculiar feeling along a roadway with sunlight slanting between trees on to their eyes. Several self-precipitated attacks have been observed by neurological colleagues in Sydney and electroencephalographic recordings made by Dr. Leonard Rail.

Intensity of the illuminant.—The dysrhythmia lessened and disappeared when the illumination was reduced. 2 patients remarked upon the lessened tendency during winter. This suggests that the condition may be absent in duller climes. On the other hand, it would seem likely that the sun, whenever shining, would be bright enough to provoke a response. The absence of the sun for long periods may prevent habit formation. Probably the condition occurs in other than the brightest lands, but less frequently.

Relationship to reflex epilepsy.—It is possible, although highly speculative, to explain reflex epilepsy precipitated by a constant visual stimulus in a similar way. Stimuli from certain objects may, for some reason, pass to the thalamus (as well as to the visual cortex) there provoking cortical dysrhythmia. Such epilepsies may be self-precipitated as in the patient reported by Bickford, Daly and Keith (1935) who stole glances at the stimulating pattern.

Treatment.—These cases showed little response to drugs of the dione group, in spite of the presence in some patients of 3 per second slow wave and spike discharges. Perhaps this is due to the intensity of the stimulus, or partly to the substitution of other dysrhythmias. However, it is in accord with the clinical observation that many patients with clinical electroencephalographic *petit mal* fail to respond to this group of drugs. Explanation of the role of the movement, and encouragement to control it, produced more result than drugs in this group.

Summary

Seven examples of photic epilepsy in which attacks were precipitated by the subject, have been described in detail.

The common feature was the precipitation of attacks by rhythmical interruption of sunlight falling on the patient's eyes. The flicker may be produced by movement of the fingers or the hand in front of the eyes, or by blinking.

The attacks were usually slight and of brief duration, with varying degrees of impairment of consciousness. If flicker was repeated for a lengthy period jactitation and major attacks might occur. In some of the patients major attacks occurred independently, but these were few.

Electroencephalograms of self-induced attacks showed varying forms of spike and slow wave discharges of high voltage, usually irregular and usually of brief duration.

Encouragement of voluntary inhibition of the provoking movement proved to be the best method of treatment.

I am grateful to Mr. A. J. Quinn, B.Sc., of the Department of Neurology and Neurosurgery, for carrying out the recordings and constructing the photic stimulator (output approximately 1 joule per flash).

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POSTERIOR FOSSA ANGIOMAS

A Clinical Presentation of Nine Cases

BY

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The advent of vertebral angiography has made the diagnosis of vascular malformations in the posterior cranial fossa possible. The purpose of this paper is to indicate the ways in which these anomalies presented clinically in nine cases, all of which were confirmed by angiography, and to show what factors might help in making the diagnosis.

A number of reports of such angiomas have appeared in the literature, although a considerable proportion of them had been accidentally discovered at post mortem, the lesion having given no indication of its presence. Teilmann (1953) in an excellent review was able to collect 42 cases, and added 3 of his own. There are, however, very few records of angiographic demonstration of these lesions during life and of their correlation with symptomatology. Sutton (1952) has described the angiographic features of 3 cases and discussed their diagnosis and Hoare (1953) reported 3 cases.

Angiomas of the posterior fossa fall into two natural groups depending on their distinct anatomical situation and symptomatology, and the case histories will be presented in these groups, which consist of:

(*a*) Cerebellar angiomas ... ... 2 cases
(*b*) Brain-stem angiomas ... ... 7 cases

In some cases in group (*b*) the angioma although predominantly of the brain-stem was not confined to that structure but had extended to involve the cerebellum.

Cerebellar Angiomas

Pathological anatomy.—Both the angiomas in this group were removed at operation so that a detailed account of their gross anatomy was obtained. Each one was found deep in a sulcus in the cerebellum and the lips of the sulcus were in each case sealed or stuck together so that the angiomas were not immediately visible on exposure of the cerebellum. In Case 2 the only indication of the lesion was staining of the cerebellar surface. The nutrient arteries were few and could be differentiated easily from the normal vascular anatomy. As will be seen, both cases presented on account of a hæmorrhage from the angioma and in each case the bleeding took place into the substance of the cerebellum and thence via the fourth ventricle into the general subarachnoid space. In many respects these lesions are very similar to the small cortical cerebral angiomas described by Mackenzie (1953).

The clinical picture.—In both instances the onset was dramatic. Neither had any previous history of serious illness, headache or neurological symptoms. Both had sudden intracranial hæmorrhages and after the initial ictus showed unequivocal signs of cerebellar dysfunction with sixth nerve paresis and transient and very mild pyramidal tract involvement.

Case 1.—I. N. female, aged 38.

Six days before admission, whilst sitting in a chair, she suddenly developed pain in the back of her head, felt dizzy and vomited several times. The headache persisted for the rest of the day and was accompanied by stiffness of the back of the neck, photophobia and pain in the back. Next morning she complained of diplopia on looking to the right and of slurring of speech. On admission at that time to another hospital she was drowsy and had severe headache. Examination revealed a right external rectus palsy, vertical and horizontal nystagmus, a minimal *right* lower facial weakness and right sided cerebellar ataxia. Lumbar puncture showed a uniformly blood-stained fluid under normal pressure. There was no previous history of serious illness and in particular none of headaches. She was transferred six days later for further investigation.

On examination on admission she had a slurring dysarthria; she was rather slow in answering but there was no definite mental impairment. A moderate degree of neck rigidity was present. The ocular fundi were normal. The right external rectus weakness and nystagmus were confirmed. Both corneal reflexes were diminished. The remaining cranial nerves were normal. A moderate degree of cerebellar ataxia was evident in the right upper limb with hypotonia and dysdiadochokinesis, and a lesser ataxia in the right lower limb. Reflexes were symmetrical and the plantar responses flexor. There was no disturbance of sensation. No intracranial bruit was heard. The B.P. was within normal limits.

Investigations.—X-ray of the skull revealed no abnormality.

Right carotid arteriography showed no evidence of a vascular lesion.

Right vertebral arteriography disclosed an enlarged right posterior inferior cerebellar artery which led to a leash of abnormal vessels on the posterior surface of the right cerebellar hemisphere. No other vessels were shown in this angiogram, and it was assumed that the angioma was abstracting blood from the left side (figs. 1A and 1B).

Ventriculography was normal and in particular there was no dilatation of the ventricles.

Operation.—A posterior fossa exploration was performed and the right cerebellar hemisphere was seen to be stained yellow. On the surface three arteries were visible running into a slightly depressed sulcus, from the right-hand margin of which a single large vein emerged. The sulcus was opened up to reveal a tortuous collection of small arteries and veins (3×2 cm.) in contact deeply with a large clot, oval in shape ($5 \times 2 \times 2$ cm.) which extended forwards and medially to the roof of the fourth ventricle. The clot and angioma were removed completely. After an uneventful recovery, further vertebral angiograms showed a normal contrast distribution.

Microscopic examination revealed the usual tortuous arterial and venous channels, which were similar in every respect to the supratentorial arteriovenous angiomas.

Case 2.—F. C. female, aged 50.

No adequate history could be obtained from her since she was very confused and no relatives were available. It appeared that about a month previously she had collapsed in the street and had been admitted to another hospital. At that time she was confused, restless and complained of severe headache. There were slurring of speech, a left extensor and right equivocal plantar response, and marked neck rigidity.

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Lumbar puncture revealed a deeply bloodstained cerebrospinal fluid under increased pressure. Further deterioration occurred during the ensuing three weeks and a well-marked cerebellar ataxia became evident in all limbs. It was also observed that the pupils were unequal, and a left sixth nerve palsy and a weakness of the left lower face were present.

Examination on admission after her transfer showed normal ocular fundi. The pupillary reactions and the external ocular movements, except for some difficulty in left lateral deviation of the eyes, were now normal. There was no nystagmus. Apart from an upper motor neurone weakness of the left face the remaining cranial nerves were normal. There was a well-marked cerebellar ataxia of all four limbs, which was more marked on the right side, and considerable truncal ataxia. The ankle-jerks were absent but the remaining tendon reflexes were equal and normal. The plantar responses were flexor. There was no sensory abnormality. No intracranial bruit was heard and there was no neck stiffness. The B.P. was 120/70.

Investigations.—X-ray of the skull was normal.

Vertebral arteriography demonstrated a mass of small vessels in the mid-line apparently situated on the cerebellar vermis and supplied from the superior cerebellar arteries (figs. 2A and 2B).

Right and left carotid arteriograms showed no abnormality.

Ventriculography revealed a small filling defect in the roof of the fourth ventricle which was otherwise normal in position. There was slight generalized ventricular dilatation.

Operation.—A posterior fossa exploration was made by turning an occipital bone flap and then incising the tentorium on the right side. Staining from previous hæmorrhage was observed over the upper vermis. This area was explored and a clot about 2 × 2 cm. in size extending down towards the fourth ventricle was removed. In the roof of this cavity an angioma made up of small vessels was found and destroyed by coagulation, after removal of a piece for section. A few days later further vertebral arteriograms showed no evidence of the angioma.

It is interesting to note that no intracranial bruit was heard in either case. The plain X-rays were normal in both cases. Ventriculography was not very helpful and only revealed a small deformity in the 4th ventricle and slight hydrocephalus in one case. The diagnosis was made absolute in both cases by vertebral angiography.

From the clinical point of view it is stressed that the behaviour of these lesions is similar to their counterparts in the cerebral hemispheres where the presentation of a small cortical angioma buried or sealed in a sulcus is that of subarachnoid hæmorrhage with gross focal signs. The diagnostic focal signs in this cerebellar group are those indicative of an acute expanding or destructive lesion of the cerebellum. We consider this group to be particularly important, since they are eminently suitable for surgery and both these patients were successfully operated upon with complete removal of the angiomas.

Brain-stem Angiomas

Pathological anatomy.—Three of the angiomas of this group were exposed at operation, and the subsequent account of the anatomy of these anomalies will be based upon observations made at the time of these

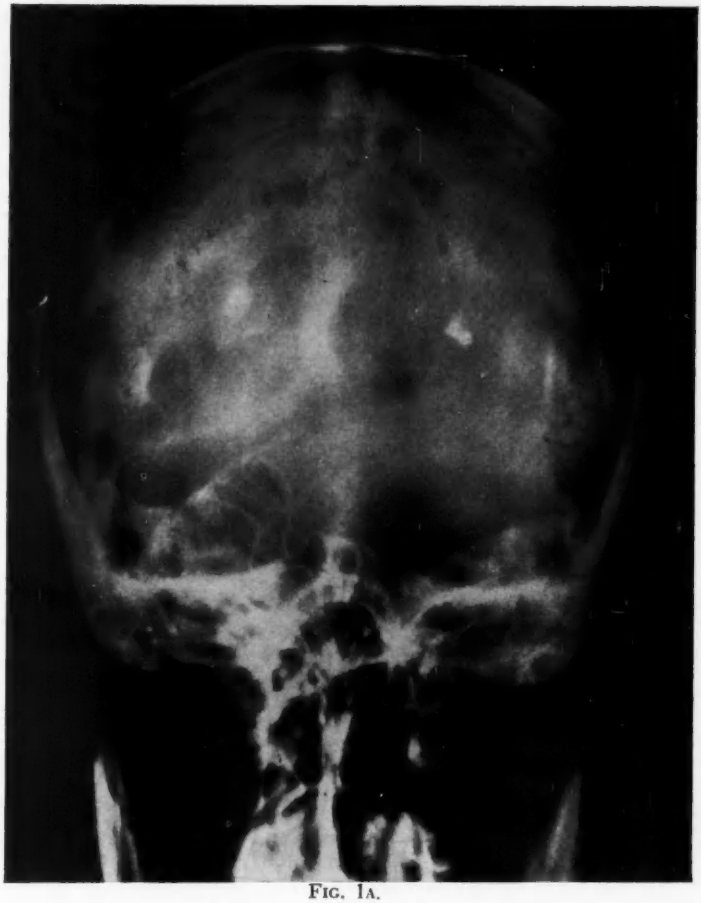

FIG. 1A.

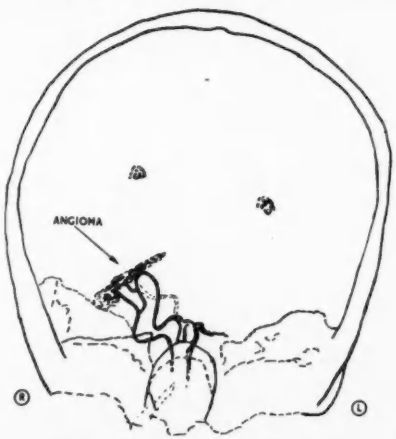

FIG. 1B.

FIG. 1A.—Vertebral angiogram A.P. view in Case 1 showing a well-defined cerebellar angioma in the right cerebellar hemisphere and outlining the main afferent supply. 1B.—Tracing of vertebral angiogram reproduced in fig. 1A.

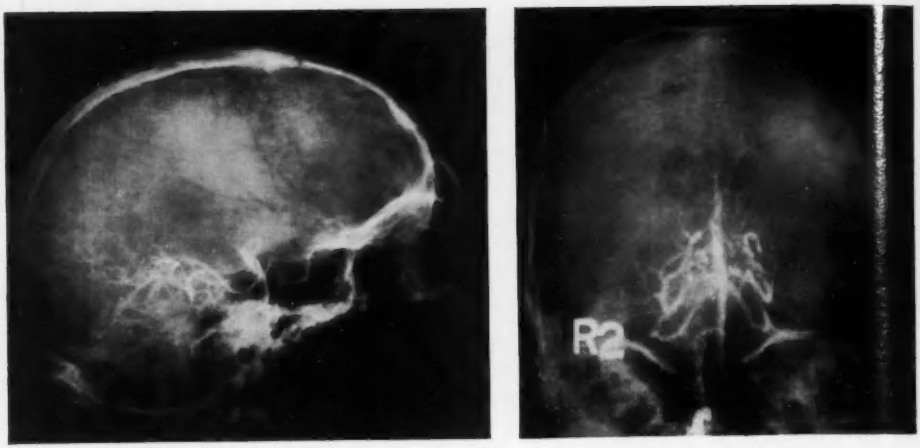

FIG. 2A.

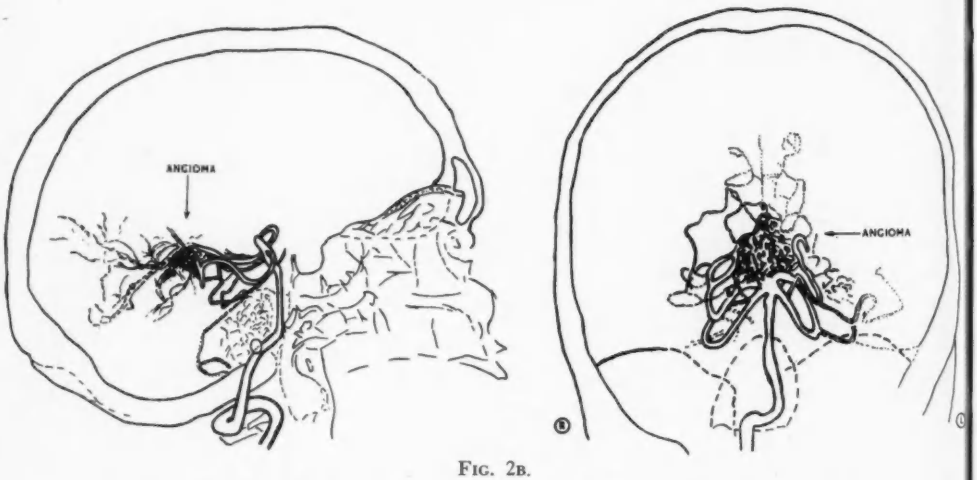

FIG. 2B.

FIG. 2A.—Showing lateral and A.P. views of vertebral angiogram in Case 2 with vermis angioma. 2B.—Drawings of angiogram reproduced in fig. 2A.

explorations. The characteristic feature of these lesions is that they appear to be an integral part of the brain-stem and are intricately woven into the normal blood supply of the hind-brain. On inspection they are seen to consist of numbers of tortuous vessels, both arterial and venous, coursing over the brain-stem and cerebellum and sending branches into the nervous tissue. Often a part of the brain-stem is pulsatile, or its substance is actually replaced by thin-walled vessels. At operation it may be impossible to

differentiate angiomatous vessels from the hypertrophied normal arteries which are supplying both brain-stem and angioma. Angiography has revealed that vascular anomalies in the cerebral hemispheres are usually much larger than appears to be the case clinically and the same is found in the brain-stem angiomas which, in our experience, are usually very diffuse, and in many cases extend from the hypothalmus to the lower pons.

The clinical picture.—Of the 7 patients in this group 5 had prolonged histories of neurological symptoms—in 2 cases as long as 15 years. In most of the cases the angiomas affected both the brain-stem and the cerebellum, but the latter structure usually to a lesser degree. The patients were admitted to hospital for one of three reasons, which were:

(1) Subarachnoid hæmorrhage ... ... 4 cases
(2) Investigation of progressive neurological disablement ... ... 2 cases
(3) Acute obstructive hydrocephalus ... ... 1 case

This forms a convenient grouping of the cases and they will be presented in this order and a short commentary given in each group.

(1) *Onset with subarachnoid hæmorrhage.*—2 of the 4 cases presenting in this way (Cases 3 and 4) had histories of previous neurological symptoms. In the other 2 cases subarachnoid hæmorrhage was the initiating symptom. In Case 5 this consisted of a single hæmorrhage, but in Case 6 at least 3 severe hæmorrhages occurred before persistent neurological symptoms and signs appeared.

Case 3.—L. E., male, aged 24.

Eight years prior to admission when attending a routine Medical Board examination it was observed that he had a tremor of the left hand and that his heart was enlarged. He served in the Navy for four years.

Four months before admission, an hour after getting up, he suddenly felt nauseated and vomited and retired to bed. At teatime he was found to be delirious and speaking nonsense. He was sent to a local hospital and he had no memory for the subsequent five weeks. Lumbar puncture showed heavily blood-stained fluid. During recovery his speech was slow and slurred and he was liable to dull headaches. On starting to get up he found his gait very unsteady and he veered to the left. It was about this time that he observed that the tremor of his left arm had become more marked. Two months before his admission, he noticed for the first time that he saw double on looking to the right. This was transient. By the time he was transferred, his speech had improved greatly, he had no headaches but was still liable to occasional nausea.

On examination he was mentally alert. The fundi were normal. The right pupil was slightly larger than the left. The external ocular movements were full with a coarse nystagmus on left lateral deviation of the eyes, and vertical nystagmus. Convergence of the eyes was accompanied by tremor of the eyelids. The remaining cranial nerves were normal. There was marked rhythmical tremor of the posturing left limbs which showed a moderate degree of hypotonia. The tendon reflexes

were brisker in the left limbs and the plantar responses were flexor. Sensory testing showed no abnormality. When walking he veered to the left. On general examination the left carotid artery pulsated more forcibly and a systolic bruit was audible in the mastoid areas, louder on the left than the right, and also over the carotid arteries. The B.P. was 120/70.

Investigations.—X-ray of the chest showed some enlargement of the heart.

Radiographs of the skull showed two large grooves on the inside of the vault running from the temporal region towards the lambda, that on the left being larger than on the right. There was notching of the arch of the atlas and enlargement of its foramina transversaria. The right jugular foramen was also enlarged.

Right vertebral arteriogram showed hypertrophy of the vertebral artery. The basilar artery was dilated and the contrast was seen to fill a large angioma of the posterior fossa, with dilated veins draining into the lateral and straight sinuses.

Left vertebral arteriogram showed the angioma to be in the mid-line, involving the pons, mesencephalon and cerebellum, and the largest entering vessel was a branch of the left vertebral artery (fig. 3).

Ventriculography demonstrated a generalized dilatation of the lateral and third ventricles, the latter being in the mid-line. The aqueduct and fourth ventricle were filled; the aqueduct showing a kink and the fourth ventricle some forward displacement, but appearing to lie in the mid-line.

Operation.—The posterior fossa was explored and the dura was found to be very tense and contained a large number of arterial channels. The right cerebellar hemisphere was normal except for a few veins running across it. The left cerebellar tonsil was replaced by an enormous vein. The posterior inferior cerebellar artery on the left was nearly three times the size of that on the right. On elevating the cerebellar hemisphere, large tortuous vessels were seen running from the basilar artery to the pons and cerebellar hemispheres. Any attempt to occlude the main arterial supply to the angioma resulted in sudden changes in the blood pressure. Nothing further was done and he was left with the decompression. He has been kept under observation for two and a half years, there have been no further subarachnoid hæmorrhages and he is at full work. The tremor persists unchanged and he is still subject to diplopia but otherwise remains well.

Case 4.—B. B., female, age 51.

Ten years before admission, she got out of bed one night and immediately lost consciousness, sustaining a bad cut over one eye. Five years before admission she had an attack of shingles affecting the right side of the face. A year before admission she again "fainted" being unconscious for a minute or two and on recovery she was nauseated and vomited frequently. Since this faint she had observed a slowly increasing weakness in her right leg. Six months later she noticed that her speech was becoming slurred. A month before her transfer she had another episode of vomiting and was taken to a local hospital.

On transfer from this hospital she was found to have a severe dysarthria, but no obvious mental impairment. The ocular fundi were normal. There was a left ptosis with normal external ocular movement. There was vertical and horizontal nystagmus, the latter more marked on right lateral gaze. A right upper motor neurone type of facial weakness was present and a left-sided peripheral clonic facial spasm. The remaining cranial nerves were normal. There was a slight cerebellar ataxia of the left arm and leg and both the lower limbs were slightly spastic. The tendon reflexes were uniformly increased but were a little brisker in the right upper limb. Sensory testing was normal. On general examination there were no abnormal physical signs and in particular there was no intracranial bruit.

Investigations.—X-ray of the skull showed well-marked thinning of the floor of the posterior fossa on the right side and the posterior clinoid processes showed

some degree of pressure atrophy. On subsequent review of the films the left foramen transversarium of the atlas vertebra was seen to be enlarged.

X-ray of the chest showed an increase in the transverse diameter of the heart.

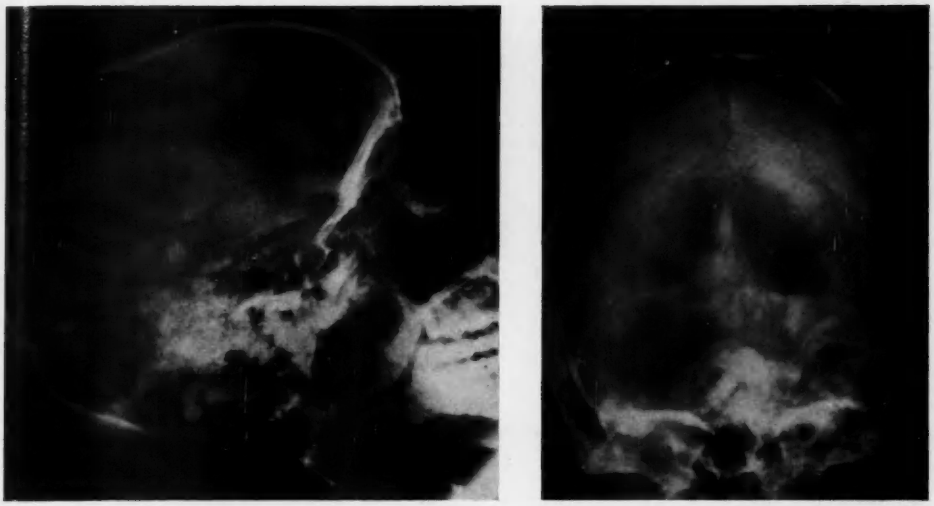

FIG. 3 (*Case* 3).—Lateral and A.P. views of vertebral angiogram showing large brain-stem angioma.

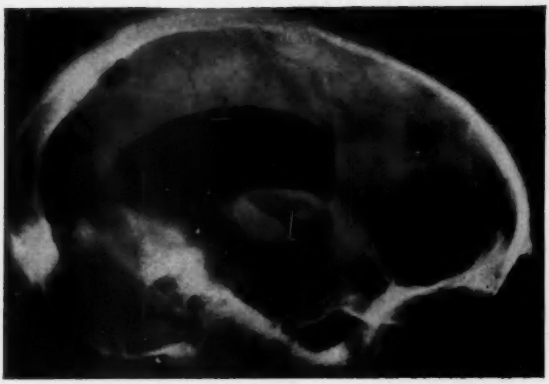

FIG 4.

FIG. 5.

FIG. 4 (*Case* 4).—Ventriculogram showing dilatation of the lateral and third ventricles. The third ventricle is grossly elevated in the posterior two-thirds of the floor and the aqueduct is not visible.

FIG. 5 (*Case* 4).—Lateral view of post-operative vertebral arteriogram showing large brain-stem angioma.

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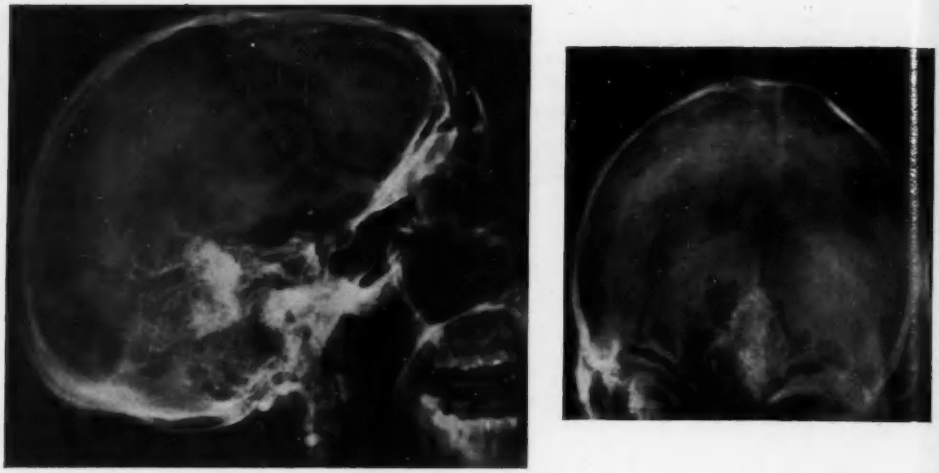


FIG. 6 (*Case* 6).—Lateral and A.P. views of vertebral arteriogram showing high brain-stem angioma.

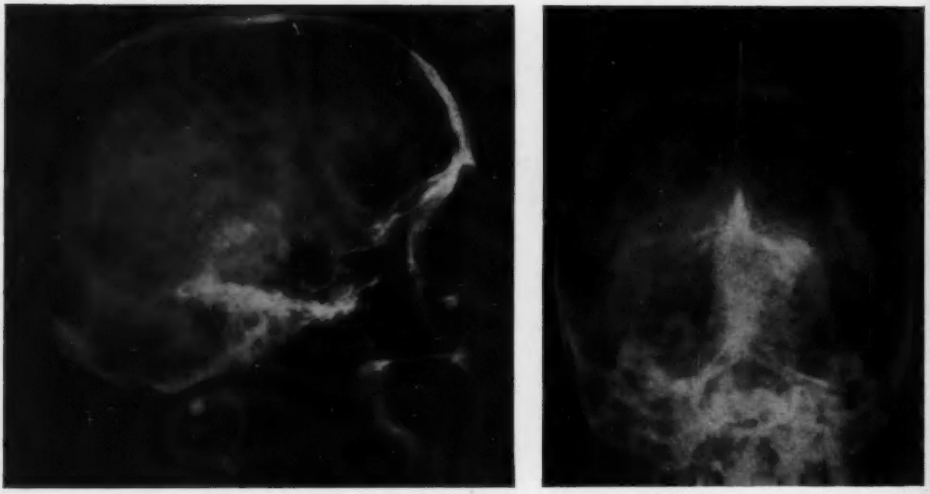


FIG. 7 (*Case* 7).—Lateral and A.P. views of vertebral angiogram showing large angioma, mainly on the left side, extending from the lower mid-brain and pons up to the hypothalamus.

Ventriculography demonstrated a symmetrical dilatation of the lateral ventricles as well as a dilated third ventricle of which the posterior two-thirds of the floor was elevated. Air could not be made to pass through the aqueduct (fig. 4).

Operation.—It was thought that the patient had a tumour in the vicinity of the

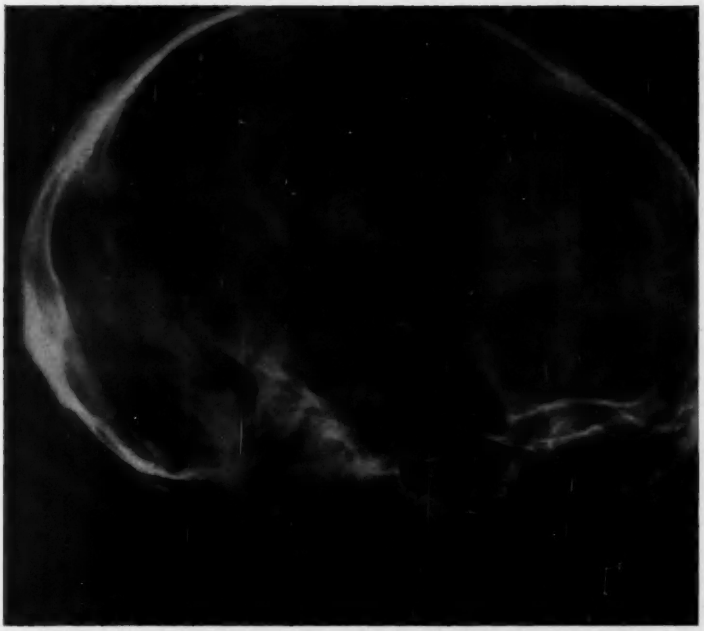


FIG. 8 (*Case* 7).—Air encephalogram showing backwards and upwards displacement of the aqueduct, slight backward displacement of the fourth ventricle. There is a filling defect of the floor of the third ventricle.

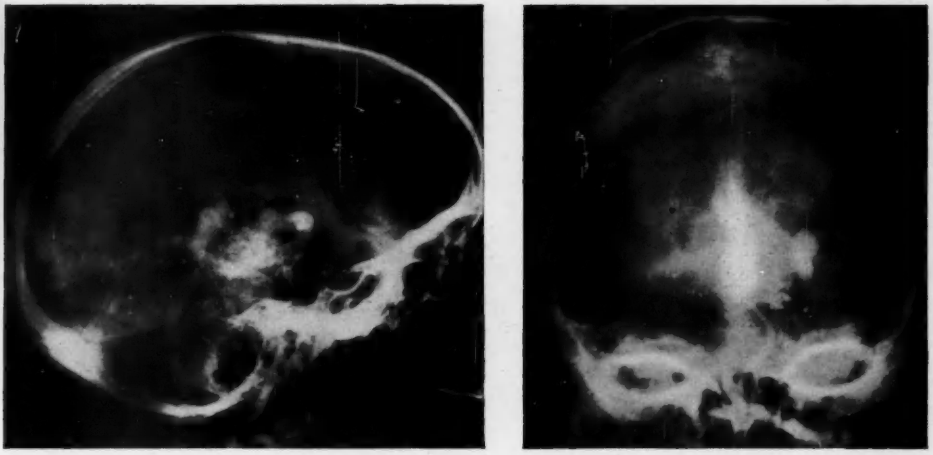


FIG. 9 (*Case* 8).—Lateral and A.P. views of vertebral angiogram showing large angiomatous mass extending from the upper pons to the hypothalamus.

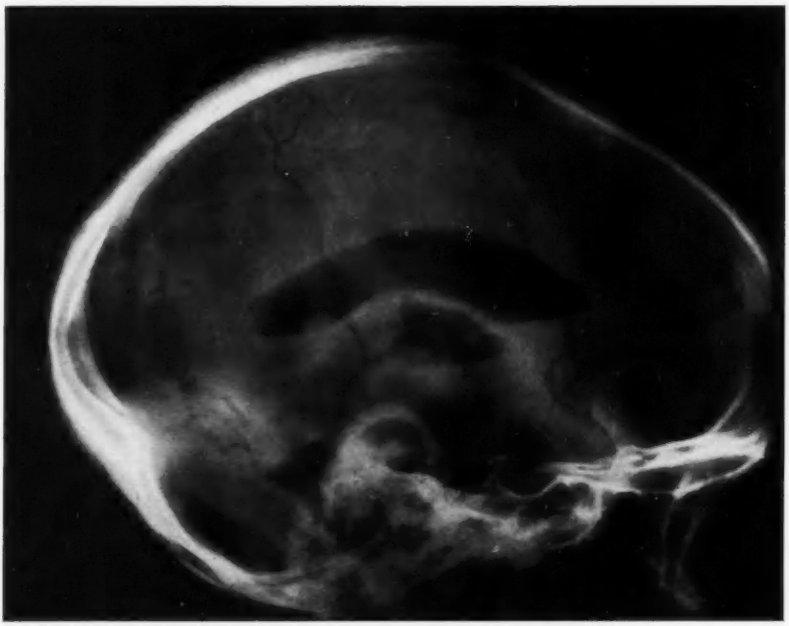
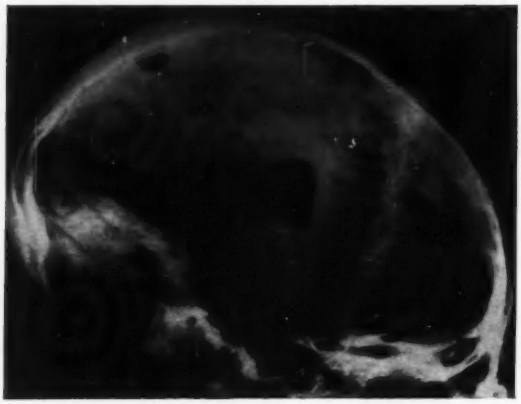


FIG. 10 (*Case* 8).—Air encephalogram showing slight backward displacement of the aqueduct and fourth ventricle. There is a suspicion of a filling defect in the floor of the third ventricle up to the mouth of the aqueduct.



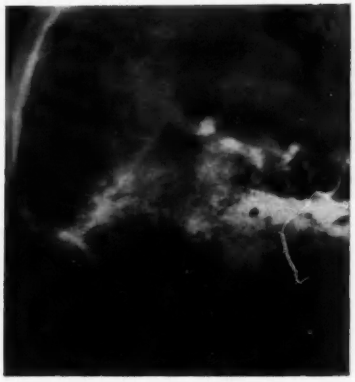


FIG. 11. FIG. 12.

FIG. 11 (*Case* 9).—Showing marked internal hydrocephalus.

FIG. 12 (*Case* 9).—Vertebral angiogram showing in lateral view the large oval ponto-mesencephalic angioma causing the hydrocephalus seen in fig. 11.

brain-stem on the left side and the posterior fossa was explored. The left cerebellar hemisphere was seen to be bulging and covered with a large number of arteries and veins running tortuous courses. Elevation of the hemisphere showed many more vessels running along the side of the peduncle and the pons. The seventh and eighth nerves were particularly involved by these vessels. Nothing further was done.

To determine the extent of the lesion a left vertebral arteriogram was performed and this showed branches of the basilar and posterior inferior cerebellar arteries supplying an enormous angiomatous mass which appeared to be filling the whole of the left half of the posterior fossa (fig. 5).

Subsequently while awaiting radiotherapy at another hospital she died suddenly.

Case 5.—B. H., male, aged 14½.

Six weeks before admission, when doing physical training at school, he was hit on the head by a "medicine" ball and felt a little dazed for a few minutes but managed to carry on. The next day he was about to begin his breakfast when he suddenly felt a severe pain at the back of his head and in his neck, and vomited profusely. His neck was stiff and he had photophobia. He was admitted to hospital the next day and he had no clear recollection of the next ten days

On examination there was no evidence of mental deterioration and no speech defect. The fundi were normal. There was a right sixth nerve palsy without diplopia. A gross coarse nystagmus was present on lateral deviation of the eyes with the quick component in the direction of gaze. There were no other abnormal physical signs in the nervous system. A systolic bruit was heard all over the præcordium. A murmur synchronous with the pulse was audible over the mastoid processes and occiput.

Investigations.—X-rays of the skull were normal.

Right vertebral arteriography demonstrated hypertrophy of the vertebral and basilar arteries and a huge angiomatous malformation occupying the major part of the posterior fossa on the right side.

Right carotid arteriography showed hypertrophy of the posterior communicating artery as far as its junction with the posterior cerebral artery and it is probable that blood was passing by this route downwards into the basilar artery and supplying the angioma via the superior cerebellar arteries. The posterior cerebral arteries were not visualized on the vertebral arteriogram. Some dilated occipital arteries were seen lying posteriorly.

No surgical treatment was undertaken in view of the size and extent of the lesion and he left the hospital.

Follow-up.—Three weeks after discharge he complained of twitching of the right side of the face and he had a right facial weakness with clonic spasms. A few weeks later he had a sudden loss of consciousness lasting two minutes, which was not followed by headache. His physical signs then consisted of a right facial weakness which increased reflexes on the right side. There was no change in the ocular signs.

A few months later his mother noticed that he was a little unsteady on his feet, and a week after this he was readmitted with a further subarachnoid hæmorrhage.

On admission he was irritable but orientated as to place. His fundi were normal. There was the same coarse nystagmus on lateral deviation of the eyes. The right pupil was a little larger than the left as part of a slight third nerve weakness. The right corneal reflex was diminished and the right face was weak. The tendon reflexes were increased on the right. There was no ataxia on formal testing. Lumbar puncture revealed a heavily blood-stained fluid. With rest in bed he made an uneventful

recovery. The right facial weakness and peripheral spasm has subsequently cleared up and he has returned to school.

Case 6.—J. B., female, aged 19.

For three years before admission she had many sudden episodes of severe headaches. These were all similar and consisted of a severe occipital headache with neck stiffness, and in retrospect it seemed probable these were all mild subarachnoid hæmorrhages. Two attacks lasted ten days and necessitated her admission to a hospital where subarachnoid hæmorrhage was confirmed, but carotid arteriography showed no vascular lesion. Two months before her transfer, she had a more severe attack and was stuporose, with papillœdema, weakness of conjugate deviation of the eyes in all directions and increased reflexes on the right side with an extensor plantar response. Following this episode she began to complain of diplopia and unsteadiness. The headache persisted in milder form and was located either in the frontal or occipital regions and her neck was persistently stiff. After transfer she continued to have more or less continuous headache but there were quite definite variations of its intensity. When it was very severe she would be drowsy and vomit repeatedly. This was taken to mean that she was having repeated small subarachnoid hæmorrhages.

On examination she was amnesic for the previous three weeks and was rather facile and euphoric. There was no speech defect. The right disc was blurred. She had a bilateral ptosis with widely dilated pupils, reacting normally. Nystagmus, with the quick phase to the left, was present on left lateral gaze and an ill-sustained vertical nystagmus on upward gaze. The remaining cranial nerves were normal. All the limbs were hypotonic and those on the right were a little weaker than the left. There was slight ataxia in all four limbs being more marked on the left. There was gross trunk ataxia so that she was unable to sit up. All tendon-jerks were diminished, right more than left, and the plantar responses were flexor. There were no abnormal physical signs on general examination and there was no intracranial bruit. The blood pressure was 130/80.

Investigations.—X-rays of the skull showed no gross abnormality.

Vertebral arteriography demonstrated a large mid-line angioma, which overlay the dorsal half of the mid-brain and was fed mainly from the superior cerebellar arteries (fig. 6).

Ventriculography showed the lateral ventricles to be slightly dilated. In lateral view the aqueduct was seen to be dilated, kinked and pressed forwards in its lower part. The pineal and suprapineal recesses of the third ventricle were obliterated. In A.P. view the fourth ventricle was displaced well to the right of the mid-line.

Operation.—A right lateral occipital flap was turned. The occipital pole was elevated and the tentorium divided. Three large arteries could be seen at the anterior margin of the cerebellum lying on the quadrigeminal plate. The angioma was burrowing deeply into the region of the inferior corpora quadrigemini, the nervous tissue being replaced by angioma vessels and pulsating. A number of smaller arteries could be seen passing farther up the brain-stem and running across the mid-line to the other side. After temporary occlusion, which had produced no symptoms, the three larger arteries which appeared to come from the superior cerebellar artery on the right were clipped and divided.

She made a slow but uneventful recovery. On discharge her physical signs consisted of a partial fourth nerve palsy on the right and nystagmus on lateral gaze. She was able to walk unaided though she was somewhat unsteady. There was minimal ataxia in the left upper limb.

Follow-up.—She has been seen from time to time during the past two years and apart from occasional headaches and nausea remains well and has had no further subarachnoid hæmorrhages. At the present time she is working as a waitress in a cafe.

In each of these 4 cases the extent of the angiomatous masses was well shown by vertebral angiography, although, in company with those angiomas to be described later, the detail of the supplying vessels was obscured by the complexity of the vascular pattern, the large draining veins overlying the tumour in different planes and, in the lateral view, the density of the petrous and mastoid temporal bones. 3 of the 4 cases were investigated by air studies. In 2 of them the angiomas were mainly posterior to the brain-stem and caused a forward displacement of the aqueduct (Cases 3 and 6). In Case 4 there was complete obstruction of the aqueduct with gross hydrocephalus. The ages of onset of symptoms in these cases was 16, 50, 14½ and 16 years respectively. The 3 youngest patients had some distortion of the aqueduct and only mild dilatation of the ventricles, whereas the oldest in the group had a marked hydrocephalus.

(2) *Patients suffering from progressive disablement.*—There are 2 cases in this group, both of which are of considerable interest and present some difficult problems. Both had extremely long histories, each of fifteen years, and neither had experienced a subarachnoid hæmorrhage. In spite of the length of history and steady progress of their disablement, there was no involvement of sensory tracts, although there was considerable motor weakness.

Case 7.—S. F., male, aged 46.

Fifteen years before admission he was discharged from the Army with weakness of his right side which progressed slowly. Four years before his admission the tempo of his illness increased, so that within four mouths he lost the use of his right arm. A year before admission, he noted drooping of his left eyelid so that the eye was all but covered. Subsequently during the year he noticed increasing weakness of the left limbs, diplopia, difficulty in swallowing and in the last six months, some disturbance of articulation.

On examination there was no evidence of mental deterioration. He expressed himself slowly owing to a marked spastic dysarthria. The fundi were normal. There was a complete left and partial right third nerve palsy and nystagmus in all directions of gaze. The right half of the palate moved poorly. He had a moderately severe right hemiparesis. The tendon reflexes were all exaggerated on the right side and there was a right extensor plantar response. A loud systolic bruit was audible over the left posterior fossa region. The B.P. was 110/80.

Investigations.—X-rays of the skull and chest were normal.

Right vertebral arteriogram demonstrated a large angiomatous malformation which lay more or less in the mid-line but spread well into the left half of the posterior fossa, and appeared to be situated in the mid-brain, extending forward into the hypothalamic region and the floor of the third ventricle (fig. 7).

XUM

Right and left carotid arteriograms showed slight filling of the anterior parts of the angioma, mainly from the left side.

Air encephalography showed the aqueduct to be displayed upwards and backwards in an arc. The fourth ventricle was also pushed back and there was a defect in the floor of the third ventricle with some degree of symmetrical hydrocephalus (fig. 8).

After leaving hospital he slowly deteriorated and developed headaches as a result of hydrocephalus, which was thought to be due to obstruction to the flow of c.s.f. at the tentorial hiatus. He was readmitted and the tentorium was divided on each side of the straight sinus. This relieved his headaches, there was some improvement in the paralysis of the right third nerve, and, rather surprisingly, slight improvement in his hemiplegia, particularly the power in his leg.

Case 8.—S. M., male, aged 48.

Fifteen years before admission he noticed that his left hand trembled when grasping for objects and that his left leg was similarly affected. Gradually, over the years, the tremor became more marked, so that on admission the movements were present even at rest. Five to six years before admission, rather suddenly he became unsteady on his feet and tended to fall to the left side. With the onset of tremor he noticed occasional diplopia, but it was not until five months before his admission that the double vision became constant, so that he saw the two images side by side but wide apart, the false image being to the right of the true. For some years past he had been subject to headaches varying in frequency sometimes several times a day, situated on the right side of the head, radiating from the right eye to the occipital region.

On examination there was no evidence of mental impairment. The fundi were normal. The pupils reacted normally but there was nystagmus on left lateral deviation of the eyes. Conjugate vertical gaze was absent and there was also a right internal rectus palsy. There was a diminution of pinprick appreciation on the left side of the face and both corneal reflexes were reduced. A static tremor of the left arm and leg was present, which was increased markedly by movement. Tone was decreased in the left limbs and power was also diminished in the periphery of the left limbs. There was gross cerebellar ataxia in these limbs on formal testing. The tendon reflexes were increased on the left but the plantar responses were flexor. There was no intracranial bruit and the B.P. was 150/90.

Investigations.—X-rays of the skull were normal.

Air encephalogram showed both aqueduct and fourth ventricle to be displaced backwards slightly beyond their normal position (fig. 10). The channel of the aqueduct appeared a little irregular. There was a suggestion of a filling defect in the floor of the third ventricle up to the mouth of the aqueduct. There was dilatation of the third ventricle in the A.P. view and the aqueduct and fourth ventricle were displaced to the left of the mid-line.

Vertebral arteriogram demonstrated an hypertrophied right vertebral artery and a large angiomatous malformation lying almost entirely on the left side around the mid-brain, but also invading its substance (fig. 9).

The right carotid arteriogram revealed some filling of the anterior part of the angioma.

Nothing further was done. He has since been seen from time to time as an outpatient and there has been little change in his condition.

Vertebral arteriography showed that the bulk of both these angiomas were in the mesencephalon, although producing an effect, as shown by

encephalography, on both the third and fourth ventricles as well as beading of the aqueduct.

These patients presented with the kind of progressive disease seen in brain-stem gliomas—but the length of history alone was such as to make that diagnosis very unlikely (Sutton 1953). The length of history must debar most kinds of benign space-occupying tumours in the posterior fossa since raised intracranial pressure would have asserted itself much earlier in the history.

(3) *A patient presenting with acute hydrocephalus.*—This patient had a two-year history of variable diplopia. The variation in the symptoms and response to prostigmine led to a diagnosis of myasthenia gravis. It was not until he developed a persistent third nerve palsy that he was admitted to hospital for further investigation. Lumbar puncture revealed a pressure of 240 mm. While in hospital acute obstructive hydrocephalus supervened.

Case 9.—I. I., male, aged 22.

Early in November 1948, he had momentary diplopia. Two weeks later the diplopia returned and remained intermittently for the next fortnight. During the succeeding eighteen months this diplopia recurred with increasing frequency and in the six months preceding admission it was constant. In February 1949 a diagnosis of myasthenia gravis was made at another hospital, and prostigmine treatment was prescribed, which the patient felt caused improvement. In September 1950 he developed a left ptosis and the right pupil was larger than the left. He was admitted to another hospital and a lumbar puncture was performed which showed the cerebrospinal fluid pressure to be 240 mm. On October 7, he suddenly developed a severe frontal headache with vomiting. The left pupil became widely dilated and did not react to light. He was then transferred for further investigation.

On examination he was drowsy but co-operative. The ocular fundi showed early bilateral papillœdema. He had a right third nerve paresis and a left partial sixth nerve palsy. There was paralysis of convergence and marked bilateral ptosis. The remaining cranial nerves were normal. He had a minimal right hemiparesis with increased reflexes on this side, with, however, bilateral flexor plantar responses. The sensory system was normal. There was no bruit on ausculation of the skull, but he had a painful rigidity of the neck. The B.P. was 120/80.

Investigations.—X-ray of the chest was normal.

Radiographs of the skull were thought to show no abnormality but subsequent review revealed enlargement of the foramina transversaria of the atlas.

Ventriculography showed a gross dilatation of both lateral ventricles and of the third ventricle. There was elevation of the floor of the third ventricle and backward and upward displacement with stretching of the aqueduct. There was a less marked backward displacement of the fourth ventricle. These findings were indicative of an expanding lesion in the region of the pons and mesencephalon causing an internal hydrocephalus (fig. 11).

Right vertebral arteriography showed good filling of the vertebral and basilar arteries. The basilar artery was hypertrophied and its two main branches entered a large oval infratentorial angioma. It measured 4·3 cm. by 6 cm. and appeared to be drained by one vein into the straight sinus (fig. 12).

XUM

Operation.—An anterior ventriculostomy was performed and the obstruction relieved since it was clear that most of his symptoms were due to the hydrocephalus. Since his discharge from hospital he has been able to return to work as a hospital porter.

The early history of this patient is interesting, in that it appears to be an example of the clinical type of presentation of relapsing symptoms and signs which may in some cases resemble disseminated sclerosis.

Discussion

In the present series all the lesions were examples of cavernous or arteriovenous vascular anomaly and the rare telangiectatic type of vascular malformation, which is often of microscopic proportions and usually symptomless, is not represented.

In a recent discussion on the problem of differential diagnosis of posterior fosa lesions Paterson (1953) referred to the difficulties in the diagnosis of angiomas in this situation, and emphasized that their clinical effects were apparently of the same order as those produced by supratentorial angiomas; they may bleed into the subarachnoid space, and by hæmorrhage, or in other ways, cause temporary or permanent interference with the functions of the nervous structures which they surround or in which they are embedded. Analysis of the cases in this series helps, in some measure, to clarify the natural history of these posterior fossa lesions.

The 2 cases of cerebellar angioma, both in women, appear to have a fairly clearly defined picture, which seems to be a product of their location and pathological anatomy. Apart from ocular paresis, the cases that we have described in this group closely parallel in symptomatology those small cortical supratentorial angiomas which produce a subarachnoid hæmorrhage in association with focal signs of brain damage, as described by Mackenzie (1953) in a paper on the presentation of angiomas of the cerebral hemispheres. The clinical picture in these 2 cases was one predominantly of cerebellar apoplexy, with subarachnoid hæmorrhage combined with paresis of the sixth cranial nerve, the latter probably being due to the subarachnoid blood, and transient mild scattered signs of pyramidal tract involvement. The air studies in each case showed very little abnormality, the only change being in Case 2 where there was a slight indentation of the roof of the fourth ventricle with slight hydrocephalus. The angiograms indicated that the lesions were well localized and in each case it was possible to point out the major artery of supply; in Case 1 the entire afferent circulation of the angioma was demonstrated (figs. 1A and 1B).

On the other hand the angiomas of the brain-stem as seen in this series have a more pleomorphic presentation, as a result of their pathological anatomy. They may be compared with those cerebral angiomas which involve the major part of a lobe of a hemisphere and so are inextricably part of the brain substance, as opposed to the cortical variety which have a superficial relationship to the brain. Their symptomatology is also similar. Both may present as a subarachnoid hæmorrhage with or without focal signs of damage to brain tissue. Both may present as progressive paralysing disease. The brain-stem angiomas, however, will, of course, differ in that they do not produce epilepsy (although transient loss of consciousness was experienced by patients 4 and 5), and owing to their special situation they may involve the cranial nerves, usually one or more from the third to the eleventh, and will also have a tendency to obstruct the c.s.f. flow either in the aqueduct of Sylvius or by blockage of the circulation through the tentorial hiatus. Thus in the 6 cases investigated by air studies there was some degree of ventricular dilatation with, however, few symptoms of raised intracranial tension, except for patient 9 who developed an acute hydrocephalus and patient 7 who eventually developed hydrocephalic symptoms after 15 years. In only 3 of the patients was there an intracranial bruit and none of them was aware of the noise.

The clinical presentation of these brain-stem angiomas and their localization can now be considered in more detail.

With regard to the age of onset of the disease it will be seen that the first symptoms occurred in the 7 patients at 16, 50, 14½, 16, 31, 33 and 20 years of age respectively. That is to say in more than half the initial presentation appeared in the second decade of life. On the other hand the length of history before a positive diagnosis of angioma was made was eight years, one year, six weeks, three years, fifteen years, fifteen years and two years respectively.

In the group admitted on account of subarachnoid hæmorrhage the clinical picture was one of apoplexy with focal signs referable to the brain-stem, an exception being Case 6 in which a considerable time elapsed before the latter signs appeared. Case 5 is of particular interest for the hæmorrhage occurred after a slight head injury, an association to which Symonds (1948) has drawn attention. Of the focal signs the ocular abnormalities are important. These may consist of nystagmus of marked degree sometimes in the absence of cerebellar signs in the limbs, and often in association with ocular palsies of a type not usually attributable to the effects of blood in the c.s.f. Cerebellar ataxia occurred in three of the cases (3, 4 and 6) but in each patient there were other brain-stem signs.

Despite these focal signs it would be difficult to localize these angiomas accurately on clinical grounds.

In the second group of cases—those with very long histories—the clinical localization would appear to be simpler and in both cases the lesions could be placed with some degree of accuracy in the mesencephalon. As we have seen, such a localization, though accurate up to a point, nevertheless only tells part of the story, since both angiomas extended from the pons to the hypothalamus. An interesting feature of both these patients was the fluctuating tempo of the progression of the illness.

In the case presenting with hydrocephalus the location of the lesion to the mid-brain could be made quite well on clinical grounds, but its pathological nature, although suggested by the intermittency of the earlier symptoms, could have been diagnosed only by vertebral arteriography.

From a review of these 7 cases, and of those reported in the literature, it is possible to give in general terms a description which encompasses much of the wealth of symptomatology that these tumours present. Thus there is a slow, sometimes fluctuating, progression of symptoms related to the cranial nerves from the third to the eleventh, irritative or paralytic, combined with disabilities in the limbs due to pyramidal tract involvement, or a tremor, or cerebellar ataxia. Giddiness and dysarthria are less common features, and in our cases the eighth cranial nerve and the long sensory pathways were not affected.

At any time a subarachnoid hæmorrhage may occur, sometimes repeated and severe, but rarely fatal, which increases, or extends the focal brain-stem signs, and although in some cases there may be as long as fifteen years without such a vascular accident, the majority of patients experience them at some stage. In a small number the hæmorrhage is the initial symptom, which ushers in the subsequently progressive signs of brain-stem involvement.

Hydrocephalus is a slowly progressive concomitant of these tumours and although few symptoms of raised intracranial tension may be present, occasionally evidence of an acute obstruction of the c.s.f. pathway may demand urgent relief. A bruit is audible in about one-third of the cases.

One point worthy of mention is that except where frank subarachnoid hæmorrhage or obstructive hydrocephalus had occurred, headache of any variety was not a prominent feature of the symptomatology.

Differential diagnosis.—In considering the differential diagnosis of angiomas in the posterior fossa it is felt that the chief difficulty will be met with that group affecting the brain-stem. As we have seen, the pre-

sentation of the cerebellar group is such that little difficulty in diagnosis is likely to arise except in those cases of spontaneous intracerebellar hæmorrhage as a result of vascular hypertension, but even then the history or evidence of long standing hypertension should clear up the problem.

In the brain-stem angiomas the diagnosis will not as a rule be difficult. In those cases where a subarachnoid hæmorrhage is superadded to previous symptoms and signs referable to the brain-stem or where the hæmorrhage is shortly followed by such symptoms, there can be little doubt about the diagnosis. Again in patients who present for the first time with a history of progressive brain-stem symptoms lasting a number of years, the diagnosis of an angioma is nearly certain, as patients with glioma of the brain-stem very rarely live more than two years, the majority less than one year. An audible bruit will of course clinch the diagnosis in any mode of presentation. It will be in two types of clinical presentation that positive diagnosis will be difficult. The first is where the angioma gives rise to subarachnoid hæmorrhage as its sole symptom with a long interval before focal signs appear, as in our Case 6. In this sort of case the diagnosis will be made, possibly fortuitously, in the routine investigation of the subarachnoid hæmorrhage, by vertebral arteriography, probably after carotid arteriography has failed to disclose a source for the bleeding. And it is of some practical importance to bear in mind when investigating cases of subarachnoid hæmorrhage without focal signs that a brain-stem angioma can produce such bleeding as the sole manifestation of its presence.

The second group consists of those cases presenting with signs indicative of involvement of the pons or mesencephalon, unilateral or bilateral, which are seen early, and before a subarachnoid hæmorrhage has occurred. If the symptoms fluctuate or are intermittently progressive it is very suggestive evidence that the lesion is an angioma, although in the early stages the condition may be confused with disseminated sclerosis, to which pitfall Martin (1951), Heirons (1953) and Teilmann (1953) have drawn attention. However, the subsequent progression of the disease, without retrobulbar symptoms and with neurological damage confined entirely to the brain-stem, with no foci elsewhere in the nervous system, should soon clarify the diagnosis.

Those cases which follow a steadily progressive course will mimic exactly a brain-stem glioma, when a clinical distinction in the absence of a bruit will be impossible, and the diagnosis will have to depend entirely on vertebral angiography, which should be employed in all cases in which a diagnosis of tumour of the brain-stem is made.

XUM

Radiology.—Sutton (1952) and Hoare (1953) have described the detailed radiological appearances of the brain-stem angiomas and the latter author has emphasized the changes which may be evident in the plain X-rays and may suggest the diagnosis before recourse to angiography. These changes consist of:

(i) Increased vascular markings in the posterior part of the skull vault,

(ii) Enlargement of the foramina transversaria in the upper cervical vertebræ,

(iii) Widening of the groove for the vertebral artery in the arch of the atlas, and

(iv) Enlargement of the jugular foramen.

Surgery.—The surgical treatment of these lesions needs brief reference. In the case of the small purely cerebellar type of angioma, as mentioned earlier, a complete surgical removal can be obtained.

With the brain-stem variety a total removal of the angioma is not feasible owing to its diffuse spread and its intimate association with the normal and essential blood supply to the brain-stem and cerebellum.

Nevertheless in selected cases (our Case 6) it may be possible to clip or ligature some of the main vessels and to prevent, for a time, a tendency to subarachnoid hæmorrhage and possibly arrest the progress of, and even temporarily improve, the neurological disability. Division of the tentorium may be of help in the mesencephalic tumours with ocular palsies (Case 7) and an anterior ventriculostomy will relieve obstructive hydrocephalus (Case 9).

Four of the patients were admitted to the Maida Vale Hospital and we are grateful to Dr. Douglas MacAlpine, Dr. S. Nevin and Dr. R. A. Henson for making their cases available to us. The remainder of the patients were under the care of one of us (V. L.) at the Atkinson Morley (St. George's) Hospital.

We are greatly indebted to Dr. James Bull, Dr. David Sutton and Dr. R. D. Hoare for many of the radiographs. (The radiological features of Cases 3, 4 and 9 have been described by Dr. Hoare in *Acta Rad.*, 1953; and Cases 6 and 8 by Dr. D. Sutton in *Arch. Middlesex Hospital*, 1952.)

Summary

Nine cases of angiomas in the posterior fossa, all confirmed by vertebral arteriography, are described, of which 2 were located in the cerebellum and 7 in and about the brain-stem.

The clinical presentation of the 2 patients with cerebellar angiomas

was that of cerebellar apoplexy with mild sixth nerve involvement and scattered pyramidal tract signs.

The 7 cases of brain-stem angiomas presented in 3 different ways:

(1) Subarachnoid hæmorrhage ... ... 4 cases

(2) Progressive neurological disablement (extending over fifteen years) ... ... 2 cases

(3) Acute obstructive hydrocephalus ... ... 1 case

The general neurological picture was that of a progressive disorder, sometimes fluctuating or intermittent, of the third to the eleventh cranial nerves, irritative or paralytic with, in the limbs, symptoms of pyramidal tract involvement or cerebellar ataxia or tremor. The eighth cranial nerve and long sensory pathways were not implicated in these 7 cases. 4 of the patients had subarachnoid hæmorrhage; 3 had an intracranial bruit.

The differential diagnosis is discussed and the surgical treatment available for certain of the lesions is referred to.

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CERVICAL SPONDYLOSIS

Incidence and Implications

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"Or ever the silver cord be loosed . . ." Ecclesiastes xii, 6.

Introduction

Cervical spondylosis (or chronic degenerative disease of the cervical spine) is nowadays a frequently made diagnosis. This is scarcely surprising in view of the plausible interpretation it gives of a number of common but previously rather obscure clinical disorders. The majority of disturbances in the territory of the cervical roots, formerly labelled "brachial neuritis" or "neuralgia," are now attributed to osteoarthritis in the neck. More recently still, largely as a result of the increasing use of myelography, cervical spondylosis has become accepted as a frequent cause of spastic paraplegia in the elderly. Forms simulating amyotrophic lateral sclerosis and others presenting with gross sensory ataxia in the upper limbs have also been described. The disease is very common and may in fact be the commonest cause of disorders of the spinal cord or cervical roots seen in the neurological practice of a general hospital.

The current views of neurologists and neurosurgeons about cervical spondylosis have not as yet gained ready acceptance in most textbooks of general medicine. This may be due to the fact that many clinicians are loath to attribute special importance to what is, after all, an extremely common radiological finding. Many people have their necks x-rayed nowadays and "spondylosis" is frequently detected. There is a prevalent assumption that such lesions are as inevitable as arteriosclerosis and a feeling that their study will prove unrewarding. The results are unfortunate. Diagnoses of "cervical osteoarthritis" are too often accepted without the various components of the radiographic picture being fully analysed. The clinical findings are then difficult to interpret.

Detailed clinical and radiological studies of asymptomatic cervical spondylosis do not seem to have been attempted. Yet until the facts about persons so affected are ascertained it will always prove difficult to assess the

significance of our patients' complaints. We will lack a background against which to view them.

Scope of the Inquiry

Opinions differ as to the incidence of cervical spondylosis in elderly people. Amongst radiologists there is general agreement that degenerative changes in the cervical spine are common after the age of 50. Actual estimates vary considerably because of the different criteria adopted in making such a diagnosis. There is, moreover, little agreement as to the possible significance of the changes observed and this is a further source of confusion.

On the clinical side, little is known of the early semeiology of cervical spondylosis. It is generally assumed that the vast majority of persons so affected have no symptoms and show no abnormal physical signs. There is little available information as to the frequency with which the nervous system is affected in this condition.

It is obvious that the most useful information on these and related problems will be derived from a study of elderly persons without symptoms of neurological illness. We here report a combined clinical and radiological survey of a group of such persons. It is our contention, based on a correlation of clinical and radiological data, that certain physical signs, skeletal or neurological, permit a diagnosis of cervical spondylosis. We believe that involvement of the nervous system in this condition occurs far more frequently than is usually thought and that the neurological complications of the disorder can be recognized before they conform to the well-known syndromes of frank root or cord compression. Asymptomatic cervical spondylosis can frequently be diagnosed clinically.

Material and Methods

Fifty in-patients of the medical and surgical wards of a teaching hospital, all aged 50 or over, were examined clinically and their necks were radiographed. Table I gives details of their age and sex and of the conditions necessitating their admission to hospital. Patients whose presenting symptoms were "neurological" were deliberately excluded

Table I.—Composition of Sample

Diagnosis		*Sex*		*Age*	
"Blood" diseases	7	Males	25	Over 65	25
Cardiovascular disease	10	Females	25	Under 65	25
Pulmonary disease	10				
Gastro-intestinal disease	11				
Others	12				
Total	50		50		50

XUM

from the survey. The social composition of the sample was representative of the hospital practice of an industrial city.

Each patient was first subjected to a joint examination by two of us (J. D. S. and C. P.). Careful records were kept of the mobility of the neck in various planes, of the presence or absence of palpable crepitus, and of any abnormal motor or sensory signs in the upper limbs. Particular attention was given to the pattern of the arm reflexes. Examination of the lower limbs was confined to a search for pyramidal or posterior column signs. No attempt was made to define accurately small areas of hypalgesia in the lower limbs as it was felt that these, if present, were probably related to coincident lumbar spondylosis and therefore did not fall within the scope of the present inquiry. As each patient was examined only once, only unequivocal abnormalities were recorded, although marginal notes were made of minor departures from normal and of findings of doubtful significance.

Each patient was then radiographed, four projections being taken with the neck in the neutral position (antero-posterior, lateral, and two obliques). It was felt that a mere statement as to the presence or severity of spondylosis—without specification of the various components of the radiological picture—would not prove adequate to explain the main types of anticipated neurological abnormality. Each patient was therefore classified by one of us (A. M. J.), according to the degrees of spinal canal narrowing and of foraminal narrowing present. Although these two types of change were often associated in a given case, instances showing mainly one or other type were not infrequent. It was hoped that with the material divided in this way, correlation with evidence of cord or root involvement might prove possible.

The clinical and the radiological surveys were completely independent. Clinicians and radiologist reached their own conclusions as to the presence or absence of spondylosis in any given case. Only when the whole sample had been analysed in this way did a confrontation take place and was an attempt made to correlate the data.

Radiological Abnormalities

(1) *Canal narrowing*

The following types of radiological abnormality, present either singly or in combination, were considered possible causes of spinal canal narrowing:

(*a*) osteophytes arising at the posterior borders of the vertebral bodies.

(*b*) subluxation of one vertebral body upon another.

(*c*) loss of the normal cervical lordosis.

Posterior osteophytosis was found to be extremely common. Each case was classified in relation to this feature. Fig. 1 shows degrees of posterior osteophytosis described respectively as "moderate" and "severe." The placing of a given case into one or other of these categories was decided in accordance with the degree of radiological abnormality present at the most severely affected site. This was thought to give a more likely idea of canal narrowing (and hence of the liability to cord injury) than an assessment of severity based on the number of discs involved.

Vertebral subluxation was estimated from the alignment of the posterior margins of the vertebral bodies as seen in the lateral radiographs. It constitutes an alteration in the anterior surface of the spinal canal and was considered a possible narrowing factor. Fig. 2 shows "moderate" and "severe" degrees of subluxation.

FIG. 1.—"Moderate" (C5-C6) and "severe" (C6-C7) degrees of posterior osteophytsis.

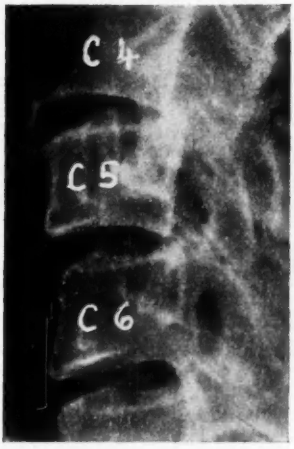

FIG. 2.—"Moderate" (C5-C6) and "severe" (C4-C5) degrees of subluxation.

Finally, *alterations of the cervical lordosis* were considered liable to affect the size of the spinal canal, particularly if associated with either posterior osteophytosis or subluxation. Experience with myelography has shown that the presence of a kyphus exaggerates the effect of posterior osteophytosis and subluxation. Alterations in the cervical lordosis were assessed as "moderate" when loss of the normal smooth lordotic curve amounted to actual straightening at any level, and as "severe" when true kyphosis occurred (fig. 3).

FIG. 3.—Loss of cervical lordosis amounting to actual kyphosis.

Having thus analysed the individual factors involved, a composite assessment of "canal narrowing" was made, in each case, as follows: Canal narrowing was considered *severe* in the presence of—

(*a*) severe posterior osteophytosis;
(*b*) moderate posterior osteophytosis + kyphosis;
(*c*) moderate posterior osteophytosis + subluxation;
(*d*) kyphosis + subluxation;

and *moderate* in the presence of—

(*a*) moderate posterior osteophytosis;
(*b*) slight posterior osteophytosis + kyphosis;
(*c*) slight posterior osteophytosis + subluxation;
(*d*) severe subluxation.

Table II (p. 279) shows the incidence of canal narrowing according to these criteria and the various mechanisms responsible.

(2) *Foraminal narrowing*

Osteoarthritis of the neurocentral joints was found to be by far the commonest cause of foraminal narrowing. Cases were classified as showing

TABLE II.—CANAL NARROWING

Incidence		*Types of abnormality in 38 patients with moderate or severe canal narrowing*	
None or slight	12 (24%)	Posterior osteophytes	34 cases
Moderate	23 (46%)	Subluxation	10 cases
Severe	15 (30%)	Kyphosis	9 cases
Total	50 (100%)		

moderate or severe neurocentral arthritis (osteophytosis) according to the standards shown in figs. 4 and 5.

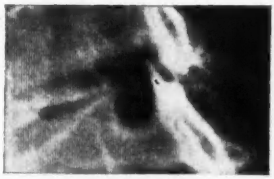

FIG. 4.—"Moderate" foraminal narrowing.

FIG. 5.—"Severe" foraminal narrowing.

Osteoarthritis of apophyseal joints may also cause osteophytic encroachment on intervertebral foramina, this time from behind, but it is not common.

Foraminal narrowing was assessed in relation to these two types of abnormality. It was graded according to the degree of involvement of the most severely affected foramen. Thus a single severely narrowed foramen would place a case in the "severe" category irrespective of the state or number of other affected foramina.

Table III shows the incidence of foraminal narrowing in this survey and the various types of lesion responsible.

TABLE III.—FORAMINAL NARROWING

Incidence		*Types of abnormality in 36 patients with moderate or severe foraminal narrowing*	
None or slight	14 (28%)	Neurocentral osteoarthritis only	31 cases
Moderate	30 (60%)	Apophyseal osteoarthritis only	3 cases
Severe	6 (12%)	Osteoarthritis at both sites	2 cases
Total	50 (100%)		

It will be noted that narrowing of intervertebral disc spaces, often a conspicuous feature of cervical spondylosis, has not been considered, in itself, as indicating a reduction in the width of either spinal canal or intervertebral foramina. 43 (86 per cent) of the examined cases showed definite narrowing of one or more disc spaces. (Narrowing of disc spaces

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occurred with the following frequency—C5–C6: 24 cases; C6–C7: 20 cases; C4–C5: 7 cases; C3–C4 and C7–T1: each 5 cases; C2–C3: 1 case.)

Marginal *osteophytes at the anterior borders of the vertebral bodies* were not considered in classifying the cases with regard to possible neurological complications. Such anterior marginal osteophytes were present in 41 (82 per cent) of our cases.

Scoliosis in the cervical spine, thought due to cervical disc degeneration, was recorded but not taken into account in assessing the presence of canal or foraminal narrowing.

Of the other radiological abnormalities noted, only one is worthy of record, namely the presence of *air in the nuclear space.* This was noted in 2 patients; one patient showed one disc affected and the other three.

On looking at lateral radiographs showing cervical spondylosis the most obvious features are often gross narrowing of intervertebral disc spaces and large anterior osteophytes. It cannot be stressed strongly enough that, immediately striking as these abnormalities may be, they are not *per se* of much importance in producing signs or symptoms. It has been repeatedly demonstrated at myelography that gross loss of disc space may occur without encroachment on the spinal canal, presumably as a result of purely atrophic changes without protrusion of disc substance.

Table IV shows the incidence of "canal narrowing" and "foraminal narrowing" abnormalities in relation to age and sex. It will be seen that, *in patients over 50, age had no significant effect upon either the incidence or the severity of these types of lesion.* It is also seen that both types of radiological abnormality are more common in men than in women. This is in accordance with the findings of other observers.

TABLE IV.—INCIDENCE OF ABNORMALITIES IN RELATION TO AGE AND SEX

	Age		*Sex*	
	>65	<65	*males*	*females*
38 *cases of "canal narrowing"*	19	19	23	15
(*a*) Moderate	12	11		
(*b*) Severe	7	8		
36 *cases of "foraminal narrowing"*	19	17	22	14
(*a*) Moderate	17	13		
(*b*) Severe	2	4		

THE CLINICAL EXAMINATION

The clinical material was divided into four groups.

Group I: 16 cases (32 per cent of the sample) without clinical abnormality of the neck or nervous system.

Group II: 4 cases (8 per cent of the sample) showing some abnormality

of the neck (crepitus, restricted movement, or both), but no abnormal neurological signs.

Group III: 16 cases (32 per cent of the sample). These showed various neurological signs, such as reflex anomalies in the upper limbs, gross unilateral or bilateral exaggeration of lower limb reflexes (with flexor plantar responses), or unexplained posterior column loss. Although these signs were unequivocal we were in some doubt as to their correct interpretation. We hoped this enquiry might determine their significance.

Group IV: 14 cases (28 per cent of the sample) with neurological signs of cord or root lesions.

(1) *The neck.*

20 patients (12 men and 8 women) out of the 50 examined showed some kind of abnormality of the neck. Restriction of neck movements was the commonest defect found (17 cases). Limitation of lateral flexion of the neck (12 cases), and of rotation (10 cases) were found more often than impaired extension (5 cases). Restricted forward flexion was not encountered. Crepitus was felt in 8 cases. It was usually associated with defective range of movement, only 3 patients showing crepitus with full mobility of the neck. It is interesting to note that three-quarters of these patients were aged 65 or over.

In 4 of these 20 cases the clinical abnormalities of the neck were the only evidence of cervical spondylosis. The other 16 showed neurological abnormalities as well, in 9 instances severe enough to justify a confident diagnosis of cord or root lesion.

It is difficult to decide what radiological criteria of spondylosis should be considered in assessing such clinical findings as restricted neck movements or crepitus. Neither "canal narrowing" nor "foraminal narrowing" types of abnormality are really appropriate yardsticks. Limitation of lateral flexion of the neck is possibly caused by lesions other than those limiting flexion and extension in an antero-posterior plane. Crepitus may well be caused by bony changes other than those we have considered, or even soft tissue changes. It is moreover probable that these signs are related to the widespread distribution of the various changes rather than to their severity at any given site, which, it will be remembered, was the basis of our classification. We can only state that 42 per cent of patients with cervical spondylosis had clinical signs in the neck—and that all those with neck signs had radiologically abnormal necks.

(2) *The nervous system.*

Abnormal neurological signs were encountered in the surprisingly high

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proportion of 30 (60 per cent) of our cases. 13 patients were under 65 and 17 over 65. Table V shows the incidence of the various findings.

TABLE V.—NEUROLOGICAL ABNORMALITIES

Group III. 16 *patients*	
Reflex anomalies in upper limbs	13
Exaggeration of lower limb reflexes with flexor plantars	2
Impaired vibration sense (one or both legs)	10
Group IV. 14 *patients*	
Absent biceps or triceps reflex	4
Extensor plantar response	6
Equivocal plantar response with brisk lower limb reflexes and/or clonus	5
Absent vibration sense (both legs)	1

Cord signs.—In Group III, 9 patients showed impaired vibration sense in one or both legs. One patient had signs suggestive of a pyramidal tract lesion and another showed both pyramidal and posterior column signs. *These abnormalities did not appear to be related to the age or sex of the patient. Moderate or severe canal narrowing was found in all* (100 *per cent*) *of these cases.*

In Group IV, there were 12 cases of presumed cord lesion. In 4 instances the clinical abnormalities were confined to the lateral columns, in one to the posterior columns, and in 7 both types of lesion were present. Six patients showed unequivocal unilateral or bilateral extensor plantar responses (of these 4 were aged 65 or over). *In this group, age appeared to have a striking effect,* 10 *of the* 12 *patients being aged* 65 *or over. Canal narrowing was demonstrable in all* 12 (100 *per cent*) *of these patients.*

It will be recalled that 38 (76 per cent) of all the patients showed canal narrowing of moderate or severe degree. Of these, 22 (58 per cent) showed signs which could be attributed to a cord lesion. In the presence of canal narrowing, cord signs were distinctly more common in the older patients (42 per cent incidence in those under 65, 74 per cent incidence in those over 65).

Root signs.—Thirteen patients in Group III showed abnormal patterns of reflex activity in the arms, often in conjunction with signs in the lower limbs. Four of the patients in Group IV were thought to have a root lesion. *Age bore no relation to the incidence of these signs* but 12 of the 17 patients were males. Foraminal narrowing was present in 10 of the 13 patients in Group III and in all 4 of the Group IV cases. No correlation could be established between the side or site of the narrowed foramen and the particular type of reflex change observed.

Foraminal narrowing of moderate or severe degree was recorded in 36 (72 per cent) of the patients radiographed. Fourteen (39 per cent) of

these patients with foraminal narrowing showed signs suggestive or indicative of a root lesion. In the presence of an adequate degree of foraminal narrowing age did not affect the incidence of such signs. Ten of the 14 patients were males.

The question immediately arises as to whether it is justifiable to attribute these various neurological signs to cervical spondylosis. The latter is a very common condition and it might be claimed that any abnormality detected primarily in the elderly would show a high correlation rate with cervical spondylosis. After 50, greying hair or arterial degeneration are probably as common as spondylosis: this does not imply any casual relationship between these conditions but merely emphasises the widespread effects of the ageing process. Our problem, however, is rather a different one. *A priori,* there are reasonable grounds for suspecting disease of the cervical spine as being capable of affecting the spinal cord and nerve roots. Age, *per se,* seems an unsatisfactory explanation for the high incidence of neurological signs and it would be difficult to interpret on this basis our 13 patients under 65 with lesions of the nervous system. A common abnormality (such as cervical spondylosis) seems more probable. We are reluctant to postulate, as an alternative explanation, certain as yet unknown neurological disorders.

More cogent evidence can be adduced, however, to strengthen the contention that cervical spondylosis is in fact responsible for the majority of these disturbances. Table VI shows the incidence of cord and root signs in canal-narrowing and foraminal-narrowing types of spondylosis—and also in persons without these skeletal abnormalities.

TABLE VI.—CORRELATION OF RADIOGRAPHIC AND NEUROLOGICAL FINDINGS

Cord signs and canal narrowing—	
Incidence of cord signs in patients without canal narrowing ...	0%
Incidence of cord signs in patients with canal narrowing	58%
Overall incidence of canal narrowing	76%
Incidence of canal narrowing in patients with cord signs	100%
Root signs and foraminal narrowing—	
Incidence of root signs in patients without foraminal narrowing ...	6%
Incidence of root signs in patients with foraminal narrowing ...	39%
Overall incidence of foraminal narrowing	72%
Incidence of foraminal narrowing in patients with root signs ...	82%

The figures are striking in the case of the so-called cord signs. *Every such patient showed canal narrowing of moderate or severe degree. Cord signs never occurred without such radiological changes.* The correlation of root signs with foraminal narrowing was less striking. Radicular signs without foraminal narrowing were a rare finding, however. Foraminal

narrowing was slightly more frequent in patients with signs suggestive of a root lesion than in others.

The value of breaking up radiological spondylosis into canal-narrowing and foraminal-narrowing types of abnormality is now apparent. Should attempts be made to relate physical signs to indeterminate osteoarthritis of the cervical spine the figures are not striking—and largely meaningless.

Only moderate or severe *bony* changes affecting foramina or canal have been considered in our tables. The possible effects of *soft tissue changes* not demonstrable radiographically have not been considered. In conjunction with slight bony defects, a given degree of soft tissue change would be more likely to affect a nerve root, in its foramen, than the cord in its wider spinal canal.

Frykholm (1951) has emphasized the importance of fibrosis of the dural root sleeve in the production of signs and symptoms. At myelography, defective filling of a root pouch may be seen without much narrowing of the intervertebral foramen. Such considerations may account for the poor correlation of root signs and foraminal narrowing.

Comments

(1) *Pyramidal signs.*—At first sight the discovery of 6 instances of unilateral or bilateral extensor plantar responses among 50 patients not thought to be suffering from any neurological disorder may seem somewhat startling. It has long been known, however, that the Babinski sign may be found in persons without symptoms or other signs of nervous disease. Wartenberg (1953) relates that Babinski himself once commented on the occasional occurrence of the sign in otherwise normal people, and that he did not then consider it as of serious significance. Critchley (1931) in his Goulstonian lectures on the Neurology of Old Age states that at times "extension of the great toe occurs in old age in the absence of obvious disease of the pyramidal pathway." Savitsky and Madonick (1943) report the examination of 2,500 patients admitted to a general hospital with a view to assessing the incidence of the Babinski sign. Many were over the age of 50, and the majority were women. Patients with conditions suggesting neurological disease were excluded. A Babinski sign was found in 4·3 per cent of these 2,500 cases. Only 1·15 per cent of 781 patients in this series, aged between 21 and 35, showed a Babinski sign. The sign was "nearly four times as common in persons over 50 as in those under 50." The same authors found extensor plantar responses in 1·25 per cent of another group of "704 inductees into the Army, between the ages of 21 and 35." In a series of conditions associated with a persistent Babinski sign, yet not causing symptoms of nervous disease, they list "old head

injuries which were not considered serious, unrecognized complications of infectious childhood disease, abortive forms of degenerative and heredofamilial disease of the nervous system, mild cerebrovascular accidents with no gross paralyses." Cervical spondylosis is not considered. Howell (1949) reports the neurological examination of nearly 200 "healthy" Chelsea pensioners aged 65 or over. 5 per cent showed "abnormality" of the plantar response and the author stresses that "such results of senile deterioration" may lead to misdiagnosis! The neck was not under suspicion in either of these large series and yet we may safely conjecture that cervical spondylosis accounted for some, at least, of these physical signs.

Sluggish lower limb reflexes are generally considered a normal feature of advancing years. In view of this, we thought brisk knee-jerks, and more particularly very brisk ankle-jerks worthy of note. Such patients were placed in Group III in view of the undetermined significance of these signs. When there was also clonus and an equivocal plantar response we felt there was stronger evidence of a long tract lesion and such cases were placed in Group IV. Altogether 13 patients were included in Groups III and IV on account of hyperreflexia in the lower limbs, clonus or extensor plantar responses (9 over 65, 4 under 65). All 13 (100 per cent) of these patients had moderate or severe canal narrowing from cervical spondylosis.

It will be recalled that canal narrowing was no more common after 65 than in the younger patients. The higher incidence of cord signs in the older age group is interesting. In such patients the duration of the narrowing might determine the appearance of cord signs. In other words continued trauma might be the significant factor. Alternatively, in patients over the age of 65, additional factors could be at work (vascular disease or "primary" senile changes, for example).

The possible role of spinal arteriosclerosis is difficult to define. Brain (1948) has discussed the significance of venous and arterial compression in the production of long tract signs in patients with cervical spondylosis and states that the "earliest changes produced by a protruded intervertebral disc are circulatory" and that such changes "must be important at all stages." If this is correct, primary disease of the spinal arteries can only accentuate the vascular disturbance. Necropsy studies in this type of disorder are very rare, however. In the cases reported by Brain, Northfield and Wilkinson (1952) the "softenings" and "destructions of normal pattern" in the cord did not appear to be particularly related to the main spinal vessels. In a detailed necropsy reported by Bedford, Bosanquet and Ritchie Russell (1952) it was emphasized that the main spinal vessels were patent and that it seemed "unlikely that ischaemia from vascular disease had played any great part in the pathology." Spinal arteriosclerosis, *per se*,

probably causes little change in the cord. Bailey (1953) has recently examined the spinal cords of a number of elderly persons without neurological signs and symptoms: although spinal arteriosclerosis was common, no correlation was forthcoming between its extent and that of the frequently observed localized glioses and atrophies of nerve fibres.

Age, *per se*, is also an unlikely factor. In the spinal cords of "normal" old people examined by Bailey (loc. cit.), slight gliosis and demyelination, often confined to the fasciculus gracilis, were frequent occurrences in the sixth and subsequent decades and were considered probably inherent to the ageing process itself. If present in more than mild degree they were to be attributed to "some cause other than senility."

(2) *Impaired vibration sense.*—Unilateral or bilateral impairment of vibration sense was found in 17 patients (10 over 65, 7 under 65). When this was the only neurological abnormality the patient was placed in Group III, when associated with definite pyramidal signs, in Group IV.

Impairment in the appreciation of vibration has long been accepted as the outstanding sensory abnormality appearing with advancing years. Pearson (1928) investigated this sensory modality in persons of all ages. After the age of 50, there was a marked change in the incidence of impaired vibration sense, the figures showing a striking increase in each successive age group considered. Explanations vary from "primary" degenerative changes in the posterior columns to "arteriosclerotic polyneuritis" (Oppenheim, Francesci, quoted by Critchley), and "sclerosing alterations in the skin, subcutaneous tissue and muscle which may interfere with the sensitivity of the sensory nerve endings" (Critchley, 1931). Spillane and Lloyd (1952) have pointed out that the reduction of this form of sensibility with age rarely develops unilaterally. No attempt has been made, that we are aware of, to correlate defective vibration sense with changes in the cervical spine. Such an attempt might prove interesting. All 17 (100 per cent) of our patients with impaired vibration sense showed moderate or severe canal narrowing due to cervical spondylosis.

(3) *Arm reflexes.*—Seventeen patients showed peculiar patterns of reflex activity in the upper limbs. An absent biceps or triceps reflex with retention of the other ipsilateral arm reflexes and of the homologous reflex on the opposite side was encountered 4 times. These patients were placed in Group IV. More frequent than such definite anomalies, however, was the finding of "dissociated behaviour" of arm reflexes: for instance gross differences between the briskness of the biceps and triceps reflexes in the same limb —or differences between homologous reflexes on opposite sides of the body. Finger flexion, on eliciting the biceps reflex, was seen several times and

occurred both with and without a contraction of the biceps itself. Complete absence of forearm flexion on testing the radial reflex was not an uncommon finding and was often associated with unusually brisk finger flexion. Patients showing such signs were placed in Group III. Foraminal narrowing was present in 82 per cent of these cases—compared with an incidence of 50 per cent in patients not showing neurological signs.

It will be noticed that bilateral sluggishness of a given reflex was not considered an abnormal sign. Howell (1949), in his previously mentioned examination of Chelsea pensioners, found absent biceps reflexes in some 15 per cent of his cases, absent triceps reflexes in about 20 per cent and absent supinator reflexes in nearly 35 per cent. From his data, however, it is not possible to deduce how often the loss was unilateral and how often dissociation occurred. Critchley (1931) states that the supinator, the biceps and the triceps-jerk become sluggish with advancing years and "may disappear, but not until after the loss of the ankle-jerks." The inference is presumably that sluggish arm reflexes with retained ankle-jerks is an abnormal state of affairs. In our experience the briskness of the radial reflexes in the elderly is variable and such variations may well be related to the integrity or otherwise of the reflex pathway in the neck. Spillane and Lloyd (1952) have discussed the significance of the reflex pattern in the upper limbs in relation to cervical spondylosis. Further observations on this point are required.

If it is accepted that the association of these signs with cervical spondylosis is not a fortuitous one, there follow certain interesting conclusions:

(1) Cervical spondylosis can be diagnosed at least as frequently by a careful examination of the nervous system as by an examination of the neck. Certain neurological signs and certain clinical findings in the neck are equally reliable indices of the disease. In this survey the former were encountered more frequently (60 per cent as against 40 per cent).

(2) Persons over the age of 50 with cervical spondylosis show a high incidence of neurological complications. This is in fact so high that it can probably be asserted that the most frequent cause of either spinal cord signs or root signs in an elderly person is cervical spondylosis. When both types of sign occur in a given case this diagnosis is the most probable one. Radiography of such a case can confidently be expected to show both canal narrowing and foraminal narrowing abnormalities.

(3) If cervical spondylosis is in fact a very common cause of neurological signs in persons over the age of 50, certain generally accepted notions about the neurology of old age require review. Much of the work in this field was done before the days of adequate radiography of the neck.

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Abnormal neurological signs are by no means an invariable concomitant of age and it is well known that the status of elderly folk in this respect is variable. Some are nimble at 80, others are already shuffling at 65. (When the locomotor disorder is out of all proportion to the impairment of the cerebral functions, cerebrovascular disease is probably not the whole story.) We suggest that cervical spondylosis may play an important part in the pathogenesis of obscure lesions of the pyramidal tracts, of impaired vibration sense in the legs, and of abnormal patterns of reflex activity in the arms of some such persons.

Summary

Fifty hospital in-patients, over the age of 50, were examined clinically and their necks were radiographed:

Of these, 75 per cent showed narrowing of the spinal canal due to various combinations of posterior osteophytosis, subluxation of cervical vertebrae and loss of cervical lordosis. After 50, neither the incidence nor the severity of canal narrowing appeared to increase significantly. Some 50 per cent of the patients with narrowing of the spinal canal showed physical signs suggestive of cord involvement. After the age of 65, the incidence rose to 75 per cent.

Furthermore, 75 per cent of the patients showed narrowing of the intervertebral foramina due to osteoarthritis at the neurocentral and apophyseal joints. After 50, neither the incidence nor the severity of foraminal narrowing increased with age. Forty per cent of the patients with foraminal narrowing showed signs suggestive of root involvement. The incidence did not increase with age.

On clinical examination, abnormalities of the neck occurred in 40 per cent and neurological abnormalities in 60 per cent of the cases. Few of the patients had complaints suggestive of nervous disorder.

Cervical spondylosis is, therefore, clearly a common disease in elderly people. Its particular importance, however, lies in the fact that involvement of the spinal cord and nerve roots may occur in a silent manner. Neurological signs may precede the development of symptoms. Certain notions about the neurology of old age require review in this light. Moreover, this concept may be of importance in explaining the unexpected, and apparently irrelevant, occurrence of cord signs in certain elderly patients.

We wish to thank our colleagues for allowing us access to patients under their care. Mr. R. Marshall, Dept. of Clinical Photography, kindly reproduced the radiographs.

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OBSERVATIONS ON REFLEX CHANGES IN THE LOWER LIMBS IN SPASTIC PARAPLEGIA IN MAN

BY

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SINCE Babinski (1911) published his observations on spastic paraplegia, it has been customary to divide the condition into two types, paraplegia-in-flexion and paraplegia-in-extension, according to which muscles, flexor or extensor, had an excess of tone. When tone predominated in the flexor muscles, the hip and knee became flexed and the ankle and toes dorsiflexed, thus approximating the limb to the trunk; when tone was greater in the extensor muscles, the hip and knee were extended and the ankle and toes plantar flexed, the lower limb being thrust out as a rigid structure. Though the distribution of tone in the muscles was the basis of the distinction between paraplegia-in-flexion and paraplegia-in-extension, associated changes in the cutaneous and other reflexes were recognized as essential distinguishing marks between the two types of paraplegia. Thus Babinski (1911) believed that exaggeration of cutaneous reflexes was only found in paraplegia-in-flexion and wrote: "L'exageration de ces réflexes cutanés constitue peut-être le caractere qui différencie le mieux les deux formes de paraplégie spasmodique." Walshe (1914) stated that the crossed extensor reflex only occurred in paraplegia-in-extension, while the crossed flexor reflex was a sign of an extreme paraplegia-in-flexion. Marie and Foix (1915) on the other hand, believed that flexor and extensor reflexes were not incompatible. They obtained well-marked ipsilateral flexor and extensor reflexes from the same limb, and noted that a flexor reflex could be interrupted by an extensor and vice versa.

Riddoch (1917) studied 8 cases of verified transection of the cord and many incomplete transections, in a group of young adults who differed from previous series by being healthy apart from their paraplegia. He observed that extensor reflexes returned after total transection of the cord, but maintained that the receptive fields for flexor and extensor reflexes were always mutually exclusive. In partial lesions the extensor reflexes were better developed, but again he observed no overlap of their receptive field with that of the flexor reflexes. Riddoch believed that there were, "no

manifestations by which we can be certain that the spinal cord has been anatomically divided," but he did think that a probable opinion could be given on the basis of the vigour of the flexor reflex and the extent of its receptive field. He maintained with Head (Head and Riddoch, 1917) that, "when an extensor reflex can be obtained from the thigh as a primary response, this great widening of the receptive field (of the flexor reflex) does not occur."

Despite the observation of Riddoch, many observers believed that the type of paraplegia indicated the integrity or otherwise of the connexions between the spinal cord and higher centres. Thus, the presence of paraplegia-in-extension was regarded as evidence that certain pathways between the spinal cord and brain-stem were intact; paraplegia-in-flexion was believed to indicate anatomical or functional isolation of the spinal cord.

The work of Sherrington (1910*a*) on the flexor reflex of the spinal dog was often quoted as supporting the view that the reflex changes in the two types of paraplegia were mutually exclusive; paraplegia-in-flexion in man was equated with the condition of the spinal dog, and paraplegia-in-extension with the decerebrate preparation. Yet a careful perusal of Sherrington's work shows that such support was not in fact forthcoming. His description of the flexor reflex of the spinal dog (1910*a*) was followed (Sherrington and Sowton, 1911) by a demonstration that modification of the stimulus applied to a sensory nerve changed the motor response obtained from a flexor to an extensor reflex. Likewise Graham Brown (1911, 1912) in a long series of experiments on the spinal cat, observed extension as well as flexion of the ipsilateral limb in response to a stimulation; he declared: "Of late it has been assumed that such phenomena as the flexion reflex and the extension reflex are specifically distinct. But in reality it may well be that no sharp line of demarcation may be drawn between." In 1912 Graham Brown and Sherrington reported their joint experience: they showed that the type of reflex response obtained from the hind-limb of the spinal dog depended largely on the site and nature of the stimulus, and emphasized that ipsilateral extensor reflexes could readily be elicited.

It was apparent that even if paraplegia-in-flexion and paraplegia-in-extension were equated with the spinal dog and the decerebrate preparation respectively, the attempt to distingush between them on the basis of the reflex responses obtained was not supported by physiological observation. The spinal and decerebrate dog differed indeed, in many respects, but both gave ipsilateral flexor and extensor reflexes in response to appropriate stimulation.

Studies of patients with traumatic spastic paraplegia since the 1939–45

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war have been more in accord with the early clinical observations of Marie and Foix (1915), and with the physiological observations of Sherrington and Graham Brown. Elkins and Wegner (1946), Pollock (1951) and Guttmann (1952) found no clear-cut distinction between paraplegia-in-flexion and paraplegia-in-extension, and were able to obtain both flexor and extensor reflexes from patients with complete transection of the cord. Kuhn (1951) made extensive studies of 29 patients with complete transection of the spinal cord verified at operation, and demonstrated that both flexor and extensor reflexes could be obtained. He found, however, that "in the present series, cutaneous stimulation proved to be relatively ineffective in the elicitation of strong extensor activity. The stimulus *par excellence* was proprioceptive in nature, preferably in the form of abrupt, passive stretch of certain large muscle groups."

Hagbarth (1952) was able to elicit ipsilateral extensor reflexes from the spinal cat by means of stimuli which were entirely cutaneous, and which did not excite proprioceptive end-organs. He also demonstrated that stimulation of the skin overlying the extensor muscles tended to give extensor reflexes, whereas cutaneous stimulation over flexor muscles produced flexor reflexes.

The present paper reports a series of observations on the reflexes obtainable from the lower limb in patients with spastic paraplegia due to disease of the spinal cord. Studies of reflex changes in spastic paraplegia due to disease is not so satisfactory as in traumatic paraplegia, for the opportunity of ascertaining the degree of interruption of spinal pathways is rarely afforded. Nevertheless spastic paraplegia due to disease is a common clinical condition, hence a re-examination of the reflex changes which accompany it, in the light of modern experience with traumatic paraplegia is desirable. Moreover, if a reflex formerly believed to be pathognomonic of isolation of the spinal cord coexists with a reflex equally believed to indicate continuity between the spinal cord and higher centres, it is clear that the significance of these reflexes requires review.

Material and Definitions

These observations were made on 44 patients with spastic paraplegia, in whom there was satisfactory clinical evidence that the lesion was in the spinal cord. The patients were not selected but were the first 44 whom it was possible to examine. The paraplegia varied in severity from those with slight weakness, spasticity and mild impairment of sensation to those with complete motor, sensory and sphincter paralysis.

Attention was mainly devoted to the occurrence of five cutaneous reflexes, though in a few patients the occurrence of extensor thrust was

also observed. The skin of the lower limbs and perineum was systematically stimulated and the incidence of the various reflexes, the nature of the stimuli required to elicit them, their receptive fields and their relationship to one another and to other signs of flexor or extensor activity in the limb were observed.

To facilitate subsequent description these reflexes will be briefly described here.

The flexor reflex.—This reflex is best elicited by a noxious stimulus applied to the skin or deep tissues of the foot, but the receptive field may extend over the whole of the lower limb even on to the anterior abdominal wall. The movements in this reflex are flexion at the hip and knee, and dorsiflexion of the ankle and toes. The Babinski response (so-called extensor plantar response) is part of the flexor reflex (Walshe, 1914).

The crossed extensor reflex occurs in the opposite leg during the elicitation of the flexor reflex. The hip and knee are extended and the ankle and toes plantar-flexed (extended). The receptive field is identical with the flexor reflex occurring in the opposite limb at the same time.

The ipsilateral extensor reflex occurs on the same side as the stimulation and consists of extension of the hip and knee and plantar flexion (extension) of the ankle and toes. Classically its receptive field is restricted to the buttock, perineum and upper fourth of the thigh, though in this study it was found possible to elicit it from a wider receptive field.

Ipsilateral flexion with extension of the foot also occurs on the side stimulated, having the same field as the flexor reflex, and consists of flexion of the hip and knee but plantar-flexion (extension) of the ankle and toes.

The crossed flexor reflex occurs in the opposite leg to the one stimulated and consists of flexion of the hip and knee and dorsiflexion (flexion of the foot). The field is the same as that of the ipsilateral flexor reflex.

Extensor thrust.—In this reflex pressure is exerted on the pads of the toes to dorsiflex them. The hip and knee extend and the ankle and toes plantar flex (extend).

The terms flexion and extension will be used in the physiological sense, flexion meaning dorsiflexion of the foot and extension being plantar flexion of the foot.

Observations

The nature of the stimulus.—The effective stimulus for the elicitation of flexor and extensor reflexes is usually described as a nocuous stimulus, implying that it threatens harm to the body. This in general was found to be true with certain exceptions.

The most effective stimulus for all the reflexes was dragging a blunt point such as a bodkin across the skin. This had to be sufficiently sharp, or pressed sufficiently hard, to produce a scratch upon the skin. The intensity and duration of this stimulus had a notable effect upon the type of reflex elicited. A short drag with heavy pressure almost invariably produced a flexor reflex, whereas a prolonged drag with moderate pressure produced an ipsilateral extensor reflex.

These differences are illustrated in figs. 1 and 2. Fig. 1 shows a brief

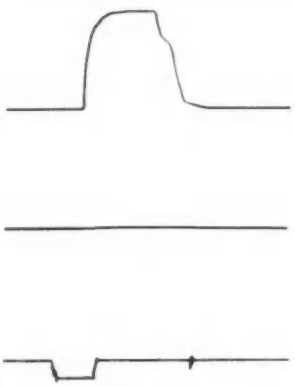

FIG. 1.

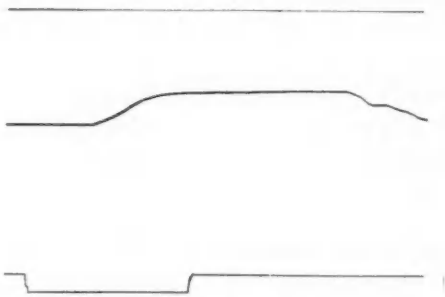

FIG. 2.

FIG. 1.—The flexor reflex. The brief stimulus followed after a short latent period by the flexor reflex. (Top, flexion; middle, extension; bottom, stimulus.)

FIG. 2.—The ipsilateral extensor reflex. The prolonged stimulus is followed after a long latent period by the extensor reflex. The reflex persists for a considerable time after cessation of the stimulus. The drum moved at the same speed as in fig. 1. (Top, flexion; middle, extension; bottom, stimulus.)

stimulus giving rise to an ipsilateral flexor reflex. The reflex follows rapidly upon the commencement of the stimulus, and subsides quickly after its cessation. In fig. 2, made with the recording drum moving at the same speed, the prolonged stimulus necessary to produce an extensor reflex is shown. The long interval between the beginning of stimulation and the start of the motor response, and the prolongation of the response after the stimulus had ceased to act, are clearly seen. These differences are typical features of the reflexes as described by Graham Brown.

Thus from the same skin area it was possible to vary the type of reflex response by adjusting the character of the stimulus. Of the two factors, intensity and duration of the stimulus, the latter seemed of the greater importance, for frequently it was possible to produce an ipsilateral

extensor reflex with heavy pressure by a very slow, prolonged drag of the stimulator.

Ipsilateral flexor and extensor reflexes were also elicited by pin-prick. A single prick, if it produced anything, invariably gave rise to a flexor reflex. Multiple pricks at a rate of about four per second, if kept initially below the threshold for a flexor response, gave rise to an ipsilateral extensor response. If the initial pricks were too hard, however, a flexor reflex developed.

Deep pressure by a pressure algesiometer also gave rise to ipsilateral flexor and extensor responses. Here again, a sudden increase in the degree of pressure gave rise to a flexor reflex, whereas if the pressure was slowly increased over a period of five to ten seconds, an ipsilateral extensor reflex followed.

Electrical stimulation was also tried, both galvanic and faradic currents being used: the latter was the more satisfactory. If the intensity of the faradic current was kept low, ipsilateral extensor reflexes were readily produced, and if a continual faradic current was applied, repeated ipsilateral extensor reflexes continued indefinitely. An increase in the intensity of the current produced a flexor reflex, as with the other types of stimulation.

All these stimuli could reasonably be described as nocuous, but the nocuous aspect of the stimulus was not indispensable. In some patients with well-developed flexor reflexes blowing on the sole of the foot was sufficient to produce a flexor reflex. Ipsilateral extensor reflexes were not obtained with such a minimal degree of stimulation. The crossed extensor reflex was never produced alone, but was an accompaniment of a flexor or extensor reflex in the opposite leg. The stimulus had to be a little more intense than that required to produce the ipsilateral flexor or extensor reflex.

Ipsilateral flexion of the hip and knee with extension of the foot was produced by a stimulus which, in intensity and duration, was midway between that required for a flexor reflex and that for an ipsilateral extensor reflex. Thus a prolonged mild stimulus might cause an ipsilateral extensor reflex: shortening and intensifying the stimulus caused the hip and knee to flex while the foot continued to extend: shortening and intensifying the stimulus even more produced a pure flexor reflex.

The crossed flexor reflex required the most intense stimulus of all. A stimulus which caused a flexor reflex with a crossed extensor reflex, when intensified, often caused the crossed reflex response to become flexor.

It was apparent, therefore, that the type of reflex elicited depended largely on the nature of the stimulus applied. The reflex response from one skin area could often be varied at will by altering the nature of the stimulus.

Receptive field of the various reflexes.—In order to compare the fields of the various reflexes the lower limb was divided into arbitrary areas, to which stimuli of different intensities and duration were applied. The sole of the foot was one area: in the leg three areas were delineated, antero-lateral, medial and posterior: in the thigh four areas were marked out, anterior, posterior, medial and lateral: the perineum and anterior abdominal wall made two more areas. The incidence of the various reflexes in these areas is shown in Table I.

TABLE I.—THE RECEPTIVE FIELDS OF VARIOUS REFLEXES

	Flexor	*Ipsilateral extensor*	*Ipsilateral flexor with extended foot*	*Crossed flexor*
Sole	88	0	3	10
Leg				
ant.-lat.	69	14	3	5
med.	66	4	3	3
post.	63	10	7	1
Thigh				
ant.	46	11	14	2
med.	43	16	10	2
lat.	37	13	14	3
post.	37	8	5	1
Perineum	13	19	3	0
Ant. abdomen	16	16	2	3

The flexor reflex was best elicited from the periphery of the limb: the more proximal the area the less easy it was to obtain a flexor reflex. Within each limb segment, however, there was no significant difference in the incidence of the flexor reflex elicited from the skin overlying the flexor as against the extensor muscles. The crossed extensor reflex had much the same field as the co-existing flexor reflex, except that it did not extend quite so far proximally as that of the flexor reflex.

The ipsilateral extensor reflex by contrast was best elicited from the proximal parts of the limb. It was also obtained frequently from the leg, but never from the sole of the foot. As with the flexor reflex there was no clear evidence that the extensor reflex was more easily elicited from skin overlying extensor muscles than from flexor surfaces.

The ipsilateral flexor reflex with extension of the foot was also more

commonly obtained from the proximal part of the limb, but on three occasions the field extended to include the sole of the foot.

The crossed flexor reflex like the ipsilateral flexor reflex was best elicited from the periphery of the limb, especially from the sole of the foot, though the field on occasion covered the whole of the limb.

A wide field for the flexor reflex was not of necessity associated with a restricted field for the ipsilateral extensor reflex and vice versa. Thus in one patient the field for the flexor reflex extended from the sole up to the groin, while that for the ipsilateral extensor reflex spread from the eleventh thoracic dermatome down to and including the medial and posterior aspects of the leg. The same skin area was frequently a part of the field of flexor and extensor reflexes, the particular reflex elicited depending on the strength of the stimulus.

When the faradic method of stimulation was used and the active electrode applied to the skin over the quadriceps femoris muscle, the possibility that the muscle was being stimulated directly and giving rise to reflex activation of other extensor muscles arose. The opportunity to examine this point was provided by a patient in whom the anterior nerve roots from the second, third, fourth lumbar segments had been divided for severe flexor spasms. When a faradic current was applied to the skin over the anterior part of the thigh with the indifferent electrode on the arm, no contraction occurred in the quadriceps femoris muscle, but flexion or extension of the foot was produced by varying strength of the stimulus. This indicated clearly that the sensory field for the reflexes was cutaneous.

Incidence of the various reflexes.—The observations on the nature of the stimulus and the fields for the various reflexes enabled a systematic exploration of the reflexes to be made, and an estimate of their incidence and interrelations to be formed; the results are given in Table II.

TABLE II.—INCIDENCE OF THE VARIOUS REFLEXES IN 44 PATIENTS

	Flexor	*Crossed extensor*	*Ipsilateral extensor*	*Ipsilateral flexor with extended foot*	*Crossed flexor*
Flexor	—	41	35	21	12
Crossed extensor	41	—	33	21	11
Ipsilateral extensor	35	33	—	17	7
Ipsilateral flexor with extended foot	21	21	17	—	3
Crossed flexor	12	11	7	3	—

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In all 44 patients a flexor reflex could be obtained by suitable stimulation at some point on the limb, and in 41 instances it was accompanied by a crossed extensor reflex. The absence of a crossed extensor reflex in 3 patients was surprising. In 1 patient the field for the flexor reflex extended up to the tenth thoracic dermatome, and a crossed flexor reflex was elicited as well. This suggested that the flexor synergy was too great to permit a crossed extensor reflex to appear. But in the other two instances a crossed flexor reflex was not present, and in 11 other patients crossed extensor and crossed flexor reflexes could both be obtained. In the second patient there were strong extensor spasms yet a crossed extensor reflex could not be obtained. In the third, the field for the flexor reflex was restricted to below the knee. There was thus no one explanation for the failure to obtain a crossed extensor reflex except, perhaps, lack of persistence on the part of the observer.

In contrast to expectation the ipsilateral extensor reflex was elicited in no less than 35 of the 44 patients, an incidence of 80 per cent. This reflex was elicited with ease by suitable adjustment of the stimulus even in patients in whom the field for the flexor reflex was extensive. In 26 patients (59 per cent) the ipsilateral extensor reflex was obtained from the lower half of the thigh or more peripherally. It should also be noted that the ipsilateral extensor reflex was obtained in 7 patients in whom the crossed flexor reflex was well developed.

Ipsilateral flexion of hip and knee with extension of the ankle and toes was seen in 21 instances in all. In 17 of these it was obtained in a limb from which an ipsilateral extensor reflex had been obtained. Thus all gradations were seen in the same patient from a pure flexor reflex, through flexion of the hip and knee with extension of the foot, to pure extension of the whole limb. In some instances these three reflexes were obtained from the same skin area by adjusting the strength of the stimulus, while in other instances they were obtained from different areas on the same limb.

A word must be said about the status of this phenomenon of flexion of the hip and knee with extension of the toe or foot. Walshe (1914) dismissed this as an artefact, believing it occurred because of contractures, or, in the case where the ankle dorsiflexed and the toe plantar-flexed, because of passive pull on the muscles of the toes. Care was taken, therefore, to avoid patients with contractures of the toes; and in cases where the toe alone extended, the ankle was held rigid, as recommended by Walshe, but extension of the toe still occurred. Moreover, in many of the patients both toe and ankle extended, excluding any possibility of passive pull on

FIG. 3.—A pure extensor movement of the foot unaccompanied by any flexion occurring in the ipsilateral flexor reflex with extension of the foot. (Top, extension; bottom, flexion.)

the muscles being caused by flexion of the ankle. This showed clearly that the extension of the toe was an active movement.

Walshe's other explanation of this phenomenon was that it constituted an abortive flexor reflex, and he published recordings showing the initial extension of the toe being followed by flexion. Fig. 3 demonstrates that suitable adjustment of the stimulus gives pure extension not followed by flexion. It seems, moreover, that following Sherrington's (1910*a*) definition of a reflex as a reaction, "in which there follows on an initiating reaction an end-effect reached through the mediation of a conductor," this extension of toe and foot, without subsequent flexion, must be considered a true reflex. The fact that a more severe stimulus may cause initial extension to be followed by flexion, does not alter the fact that a milder stimulus will produce pure extension of the foot followed by a return to the neutral position. Moreover, increasing the stimulus to one skin area produced first ipsilateral extension, then ipsilateral flexion with extension of the foot, and finally pure flexion, suggesting that ipsilateral flexion with extension of the foot is a transition phase, in which neither flexor nor extensor dominance is established.

The crossed flexor reflex was the least common of the reflexes obtained, occurring in 12 patients. In 11 of these it occurred as an alternative to the crossed extensor reflex. The ipsilateral flexor reflex with which the crossed flexor reflex was associated was usually elicited from a very wide field, but only a restricted part of that field gave the crossed flexor reflex. In 1 patient, however, the crossed flexor reflex was obtained from the whole of the lower limb.

An illustration of the occurrence of the different reflexes in the same patient is shown in figs. 4, 5 and 6. Fig. 4 shows the flexor reflex accompanied by the crossed extensor reflex following stimulation of the sole of the foot. Intensifying the stimulus to the sole of the foot changed the crossed response from an extensor to a flexor reflex as shown in fig. 5. In fig. 6 stimulation of the lower half of the lateral side of the thigh caused extension of the knee and plantar flexion of the ankle and toes in the ipsilateral extensor reflex. Fig. 7 which was taken from another patient

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FIG. 4.—The flexor reflex accompanied by the crossed extensor reflex in response to stimulation of the sole.

FIG. 5.—The flexor reflex accompanied by the crossed flexor reflex with strong stimulation of the sole, in the same patient as fig. 4.

FIG. 6.—Stimulation of the thigh causing extension of the knee and plantar flexion of the ankle and foot in the same patient as fig. 4.

FIG. 7.—A double exposure showing the extension of the ankle and toes in response to stimulation of the lateral side of the leg in the ipsilateral extensor reflex.

shows clearly the active extension of the toes and foot in the ipsilateral extensor reflex following stimulation of the lateral aspect of the leg. There can be no doubt, therefore, that these various cutaneous reflexes can be obtained from the same patient at one time, and cannot, therefore, be indicative of continuity or disruption of the spinal cord.

The relationship between tonus and reflexes.—5 patients in this series had so great an increase of tone in the extensor muscles of the lower limbs that they were held rigidly, and it required tremendous force exerted for 30 seconds or more to bend the knees in order to seat the patient in a chair. This great increase in extensor tone, however, was not accompanied by a similar preponderance of the ipsilateral extensor reflexes. In 2 of the patients these reflexes were completely absent; in 2 others they were restricted to one limb, although the extensor hypertonus affected both; and in 1 patient ipsilateral extensor reflexes were obtained bilaterally, but the field was restricted to the anterior aspect of the thighs. The ipsilateral flexor reflex in these patients, on the other hand, arose from a wide area extending in 2 on to the abdomen, and in 2 others up to the groin. In 3 of the patients the crossed flexor reflex was also obtained. There was thus no correlation between the degree of extensor tonus and the facility with which ipsilateral extensor reflexes were elicited, or with the depression of flexor reflexes. There was, on the other hand, a positive correlation between the presence of extensor spasms and well-developed ipsilateral extensor reflexes. 3 patients had extensor spasms, and in all 3 the ipsilateral extensor reflexes were readily elicitable.

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The occurrence of extensor thrust.—Only 12 of the patients were examined for the extensor thrust reflex, but in 4 of these it was found. The best method of eliciting this reflex was to dorsiflex slowly and steadily the second, third and fourth toes by pressing up against the pads, until eventually the foot was being dorsiflexed as well. It was difficult to be certain if dorsiflexion restricted to the toes would give the reflex, though the impression was that it did. As the pressure was exerted the extensors of the knee and ankle became active and thrust the leg out rigidly with the foot strongly extended (plantar-flexed). All 4 patients showed ipsilateral extensor reflexes as well, though not from a wide field. The field for the flexor reflex was restricted in 2 patients to the skin below the knee, but extended in the other 2 up to the groin.

Discussion

The observations reported in this paper lend no support to the view that spastic paraplegia can be clearly divided into two groups on the basis of the reflexes obtainable from the lower limbs. Study of the various reflexes obtained in these patients showed that all possible combinations of flexor and extensor reflexes occurred. Thus, ipsilateral flexor and extensor reflexes were frequently obtained from the same limb by applying different stimuli. A crossed extensor reflex, believed only to occur in paraplegia-in-extension, co-existed with a crossed flexor reflex, said to be typical of extreme paraplegia-in-flexion (Walshe, 1914), in no less than one-fourth of the patients. No division could, therefore, be made on the basis of the type of reflex obtainable from the limb.

Charting the fields of the various reflexes also failed to show a clear division of the cases into two groups. Thus the same skin area gave flexor and extensor reflexes with ease, depending entirely on the type of stimulation used. Likewise, a widening of the field for the ipsilateral extensor reflex was not of necessity accompanied by a corresponding reduction in the flexor field.

The factors of pre-eminent importance in determining the type of reflex obtained were the intensity and duration of the stimulus used to elicit it. A noxious stimulus, mild in degree and prolonged in duration, was the appropriate stimulus for the ipsilateral extensor reflex, whereas a severe stimulus of short duration almost invariably gave rise to an ipsilateral flexor reflex response.

Though an exclusive distinction between the types of reflex obtained, or their fields, was not observed, it must not be thought that a pattern was completely absent. The flexor reflexes, both ipsilateral and crossed, were undoubtedly most easily obtained from the periphery of the limb,

whereas the ipsilateral extensor reflex was best elicited from the proximal part of the limb. Thus, though the overlapping territory of these reflexes spread from groin to ankle, their foci, or points of maximum incidence, were at opposite ends of the limb.

No difficulty was experienced in obtaining the extensor reflexes by cutaneous stimulation, in contrast to the observation of Kuhn (1951). 2 patients who had shown no motor, sensory or sphincter activity for over four years gave flexor and extensor reflexes in response to cutaneous stimulation with ease. Similarly faradic stimulation of the skin overlying muscle incapable of a motor response, gave flexor and extensor reflexes. A predisposition of the skin over flexor muscles to give flexor reflexes and over extensor muscles to give extensor reflexes, as seen by Hagbarth (1952) in the cat, was not observed. This may well be a reflection of the fact that it is not possible to test patients with the same exhaustive thoroughness as can be done with the experimental animal. Though every effort was made to test each skin area systematically on several different occasions, the limitations imposed by the clinical situation enjoins that conclusions should be drawn only tentatively from negative results, and the main emphasis placed on the positive findings.

This demonstration of flexor and extensor reflexes co-existing in the same patient is not an abandonment of the physiological teaching of Sherrington, but rather a return to it, for the teaching of clinical neurology in this field appears to have been based on one aspect of Sherrington's views only, and to have ignored other aspects of his work, and the work of Graham Brown. Writing of the spinal dog Sherrington (1910*b*) states "the attitude thus exhibited undoubtedly amounts to standing and is sometimes maintained for minutes at a time." And though he goes on to say that, "Spinal standing is not fully equivalent to the standing of the decerebrate preparation" he clearly recognized the existence of extensor activity in the completely isolated spinal cord. The concept of a continuum existing between the dominance of flexor reflexes on the one hand and of extensor reflexes on the other was always present in physiological teaching; and the notion that the presence or absence of extensor reflexes indicated, respectively, continuity or complete disruption of spinal pathways was foreign to it.

Paraplegia-in-flexion and paraplegia-in-extension remain, therefore, as clinical entities dependent on the group of muscles in which tone predominates. The more severe the lesion the more will the tone of the flexor muscles exceed that of the extensors and vice versa. With this predominance of tone, however, there does not go an equal predominance of the type of reflex response obtained. As Riddoch observed, both flexor and

extensor reflexes may be present when tone predominates in one group of muscles; and this study would go further by demonstrating that the opposing reflexes may be elicited from the same receptive field by suitable adjustment of the stimulus irrespective of the distribution of tone in the muscles.

The observations made here are in agreement with those of observers of traumatic paraplegia since the 1939–45 war. The excitation of flexor or extensor reflexes from the skin does not depend on whether the cord is in isolation or not, for both can be elicited at one and the same time from the same patient. The determining factors as to whether flexor or ipsilateral extensor reflexes are obtained are the intensity and duration of the stimulus applied and to a lesser degree the site of its application.

Summary

The cutaneous reflexes obtainable from the lower limbs of 44 patients with spastic paraplegia due to disease of the spinal cord, together with their receptive fields and their adequate stimuli have been systematically studied.

Division of these reflexes into two distinct groups was not found, for all reflexes were present in many patients. The determining factor as to which reflexes are obtained is not the predominance of flexor or extensor tone, but the nature of the stimulus used to elicit the reflex, and to a lesser degree its site of application.

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THE DISCRIMINATION BETWEEN PINCHING AND PRESSING OF THE SKIN

The Basis of a Clinical Test

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Introduction

Tshlenow (1928) described a test in which a fold of skin is lifted between two fingers and pulled in one direction or another while the subject, with his eyes closed, has to describe the direction of skin movement. He investigated 60 patients with various sensory abnormalities and showed that the faculty of detecting the direction of skin movement, which he called cutaneous cinæsthesia, was impaired when the perception of movements of limb segments (henceforth referred to as muscle-joint sense) was diminished and this led him to postulate that the same sensory tract subserved these two forms of sensation. On the other hand he found no constant relation between defects of cutaneous cinæsthesia and defects of the senses of pain, temperature and touch. He considered that with a progressive lesion cutaneous cinæsthesia was diminished before muscle-joint sense and he concluded that a test of the former should be included in current practice of clinical examination.

Halpern (1946, 1949), unaware of Tshlenow's work, described an exactly similar test but thought that the faculty of detecting the direction of skin movement, which he called dermatokinæsthesis, was never disturbed in the presence of normal muscle-joint sense. Despite this he felt that the test was of considerable value in demonstrating sensory levels since this is scarcely possible with tests of muscle-joint sense.

On trying this method of sensory examination we found that the first patient could neither perceive clearly the pinching of the skin nor the direction in which it was pulled and it seemed to us that the loss of perception of pinch was greater than the loss of perception of direction of movement. This patient declared that he could in no way discriminate between a pinching of and a pressing on the skin and this was all the more impressive when it was considered that the diminution of muscle-joint sense was only slight. A further trial in several cases of disseminated

sclerosis revealed that a loss of pinch-press discrimination was not uncommon and we therefore decided to apply the test to a series of subjects and to correlate the results with those of other sensory tests.

Method

In the investigation a battery of tests was used and to facilitate the recording of results a form was specially designed and printed.

In an effort to standardize the tests as much as possible it was decided to restrict them to certain areas of the body. The test involving digit movement (muscle-joint sense) was confined to the terminal phalanx of the index finger and great toe. Vibration sense was tested at the wrists and ankles. All the other tests, including that of two-point discrimination, were confined to a limited area of skin on the dorsum of the hand and foot. In the hand, the area chosen lay between the first and second metacarpal bones over the belly of the first dorsal interosseus muscle. In the foot, the area chosen lay on the medial aspect of the dorsum of the foot, that is, over the first metatarsal bone. These areas were thought most suitable because the skin is freely mobile and relatively hairless; the mobility of the skin is relatively constant in different individuals; and finally the patient is able to lie or sit with his forearms comfortably pronated.

The test of pinch-press discrimination.—In this test the observer pressed the skin of the subject down firmly with the tip of his index finger or pinched the skin up between the index finger and thumb. In pinching the skin the amount of skin gripped between the fingers and the pressure applied was just sufficient to prevent the skin slipping. Care had to be taken to avoid hurting the subject although it was found that the pressure had to be relatively great before pain was produced. It was necessary, too, to avoid giving the subject a cue by the pressure of the observer's finger nails on the skin.

The pinches and presses were given in equal numbers and in a random order according to a sequence printed in the form. A total of twenty tests was made in each area. With his eyes closed the subject had to respond with the words pinch and press and at the end of the test he was given a score on the basis of his correct responses.

Before beginning the test it was found advisable in the less intelligent subject to demonstrate what was meant by a pinch and a press by applying the test a few times on the back of the hand while he watched. This also afforded the opportunity of demonstrating that the pinches were not painful.

The test of discrimination of direction of skin movement.—In this test the observer pressed the subject's skin firmly with the tip of his index finger and then moved the skin about ¼ in. to the right or left. The subject had to describe the direction of movement and his score was based on his correct responses to a random sequence of twenty movements printed in the form.

The test of discrimination of direction of movement of an object moved across the skin.—In this test the observer moved a brush across the skin in a right or left direction, the distance of movement being about ½ in. The brush was made of hog's hair and the head, which was flat, was about ¼ in. in breadth. This type of brush allowed the skin to be firmly stroked. The application and scoring of the test was similar to the previous two tests.

The test of discrimination of direction of digit movement.—In this test the terminal phalanx of the index finger or great toe was moved up or down. No attempt was made to score this test and the observer recorded his impressions as is normally done in clinical practice. Three grades of defect were recorded. The first was slight and this represented the minimal degree of defect which the observer was capable of detecting with confidence. The other grades of moderate and severe cannot be defined but are self explanatory.

The test of two-point discrimination.—An engineer's vernier caliper was used in this test. This instrument which can be purchased for a few shillings is very convenient to use and immediate readings in inches or millimetres can be made. This instrument is essentially similar in construction to the one illustrated in Finlayson's Clinical Manual (1891). The maximum reading of the caliper is 9 centimetres. The two points of the caliper were pressed on the skin in the *long* axis of the limbs and the minimum distance between the two points which the subject could detect was estimated. The method was the rough and ready one generally adopted in clinical practice and no attempt was made to pursue the precise method used by Head and his co-workers.

The test of vibration sense.—In this test a tuning fork vibrating at 128 cps was used. In general the results were recorded as normal or absent. However, when there was a significant asymmetry between the right and left limbs, the result of the test in the limb, which had a relative diminution of vibration sense, was recorded as moderate.

Material

The test of muscle-joint sense, being part of a routine neurological examination, a search was made for a patient in which this sense was

diminished while pinch-press discrimination was normal. No such patient was found.

Of the many patients who were found, in the course of six months, to have an impairment of pinch-press discrimination a selection of 50 patients was made among whom were those that showed the greatest discrepancy between muscle-joint sense and pinch-press discrimination. In some of these patients the limitation of time prevented the complete battery of tests from being applied.

Two further groups of patients were selected. The first group consisted of 2 patients with amyotrophic lateral sclerosis; 2 patients with thrombosis of the posterior inferior cerebellar artery; and 3 patients with syringomyelia. The second group consisted of 10 patients who were referred for the opinion of a neurologist and in each the condition was considered to be psychological in origin.

A control group was drawn from general medical wards and in none of these patients was neurological disease suspected. A total of 75 patients was studied. In this group an effort was made to exclude people of a nervous disposition and a decision to do so in any particular case was made before the tests were applied.

People who were very ill or mentally confused were excluded from all groups.

Results

(1) Of the 75 controls, 25 subjects were examined in both hands and feet; 25 were examined only in the hands; and 25 only in the feet. In all limbs tested, the scores in the tests of pinch-press discrimination, discrimination of direction of movement of the skin, and discrimination of direction of brush movement were 18 or more. The maximum score possible was of course 20.

In the test of two-point discrimination, most subjects could detect two points at a distance of 2·0 to 2·5 centimetres. The greatest distance was 3·0 centimetres and this was taken as the limit of normality in both the hand and the foot.

(2) The patients with amyotrophic lateral sclerosis, thrombosis of the posterior inferior cerebellar artery, and syringomyelia showed scores similar to the controls. The patients suffering from the last two disorders, exhibited severe loss of pain and temperature sense in the limbs tested.

(3) The 10 patients with psychological disorders had a marked diminution of two-point discrimination. Seven showed normal scores in the other tests, while the remaining 3, who were suffering from a hysterical paralysis of limbs and exhibited a glove-stocking anæsthesia, had poor scores in all tests in the battery.

		Pinch-press discrimination	*Discrimination of direction of skin movement*	*Discrimination of direction of brush movement*	*Muscle-joint sense*	*Vibration sense*	*Two-point discrimination*
1	Subacute combined degeneration of the cord	11	14	—	Slight	Absent	—
2	Cerebral thrombosis	10	9	—	Slight	—	7·0
3	Disseminated sclerosis	0	0	—	Severe	Absent	9·0+
4	" "	16	—	—	N	N	—
5	" "	14	—	—	N	N	—
6	" "	15	20	—	N	N	3·8
7	Subacute combined degeneration of the cord	16	18	—	N	N	4·5
8	Disseminated sclerosis	9	17	—	Slight	Absent	4·5
9	" "	10	17	—	Moderate	N	3·2
10	" "	10	20	—	N	N	1·3
11	" "	8	20	—	Severe	N	3·5
12	" "	8	11	—	Moderate	N	4·5
13	" "	8	16	—	Slight	N	6·0
14	Acute infective polyneuritis	9	17	—	Slight	Moderate	4·3
15	Cervical spondylosis	13	17	—	Slight	N	—
16	Acute infective polyneuritis	7	7	—	Severe	Absent	9·0+
17	Spinal tumour	9	10	—	Severe	Moderate	—
18	Disseminated sclerosis	12	11	16	Severe	N	9·0+
19	" "	0	0	0	Severe	Absent	9·0+
20	Tabes dorsalis	14	20	20	N	N	6·7
21	Disseminated sclerosis	15	11	20	N	N	8·2
22	" "	11	20	19	N	N	4·5
23	" "	11	9	11	Slight	N	7·0
24	" "	15	—	—	Severe	N	—
25	" "	0	10	0	Slight	N	8·5
26	" "	10	10	17	N	N	3·5
27	" "	11	19	10	Slight	N	9·0+
28	" "	13	—	—	N	—	—
29	Pontine thrombosis	0	—	—	Severe	—	—
30	Cerebral Glioma	13	—	—	Slight	—	—
31	" "	12	20	20	N	N	6·8
32	Carotid thrombosis	14	20	18	Moderate	N	*
33	Disseminated sclerosis	11	10	11	N	N	6·5
34	" "	11	—	—	Slight	Absent	—
35	Cerebral thrombosis	7	5	7	Severe	Absent	4·5
36	Subacute combined degeneration of the cord	12	14	17	N	Absent	4·0
37	Tabes dorsalis	0	0	0	Severe	Absent	*
38	Cord compression	10	14	14	N	N	3·0
39	Tabes dorsalis	14	19	20	N	N	*
40	Paraplegia undiagnosed	0	0	0	Severe	Absent	7·5
41	Diabetic neuritis	11	—	—	N	N	2·5
42	Disseminated sclerosis	0	—	—	Moderate	Absent	5·5
43	" "	10	—	—	Moderate	Absent	9·0+
44	" "	11	—	—	Moderate	Absent	6·0
45	" "	0	—	—	N	N	7·0
46	Cervical spondylosis	13	—	—	N	N	2·6
47	Disseminated sclerosis	12	—	—	N	N	9·0+
48	Cervical spondylosis	16	—	—	Severe	N	9·0+
49	Cord injury	12	—	—	N	N	—
50	Cerebral thrombosis	16	—	—	Severe	N	9·0+

A score of 10 can be obtained by guessing and therefore represents the lowest score. A score of 0 is given when the patient said he was unable to guess.

(4) The results obtained in the 50 selected cases are shown in the table. It is not possible to tabulate all the results and, for the sake of brevity in this report, a limb is selected in each case. The limb chosen is the one which revealed the greatest discrepancy between the results of the tests of joint sense and pinch-press discrimination, although, it must be noted, that in all limbs a diminution of muscle-joint sense was associated with a diminution of pinch-press discrimination.

The table shows that in most cases a severe diminution of muscle-joint sense was associated with a very low score in the test of pinch-press discrimination. There were three exceptions, cases 24, 48 and 50. The only feature common to these three cases was a regression in the physical signs. In the majority of the other cases the condition was probably progressing although this cannot be stated with any certainty. In Case 50 the test of pinch-press discrimination was applied to the soft tissue of the fingers and the score was found to be much lower than on the back of the hand.

The table also shows that two-point discrimination was always diminished when muscle-joint sense was impaired. In the cases marked with an asterisk, the patient responded to the application of one and two points indiscriminately and no measurement could be made.

When the loss of muscle-joint sense was severe there was nearly always a diminution in the discrimination of the direction of skin movement and brush movement. With the milder grades of muscle-joint sense defect the scores in these two tests were occasionally within normal limits.

(5) There was no correlation between a loss of vibration sense and the results of the other tests. In several patients a loss of vibration sense was the only sensory sign but these were not included in the series.

(6) It must be repeated that in all patients a loss of muscle-joint sense was accompanied by a loss of pinch-press discrimination in the same limb.

(7) In the last three months of the investigation no patient was found in whom a loss of muscle-joint sense was not accompanied by a diminution of two-point discrimination in the same limb.

(8) It is evident from the table that the great majority of patients showed a diminution of two-point discrimination. There were, however, three exceptions.

Discussion

In describing his test Tshlenow stated that the degree of displacement of the fold of skin was an important factor in influencing the patient's responses. The range of movement is obviously crucial in tests involving the passive movements of limb segments and it seems safe to generalize

that, in all tests of the perception of direction of movement, the range of movement has to be standardized. This is extremely difficult, especially in the movements of limb segments because muscular relaxation and joint mobility vary greatly between patients. In the test of pinch-press discrimination it was found that the size of the fold of skin held between the fingers did not, within wide limits, materially affect the patients' scores. This test was therefore to be preferred to the other movement tests in our battery, apart from the fact that in practice it proved to be the most sensitive.

The correlation of defects of pinch-press discrimination and those of muscle-joint sense largely confirms Tshlenow's observations with regard to his own test, that is, pinch-press discrimination and cutaneous cinæsthesia become impaired before muscle-joint sense in the presence of a progressive lesion. Tshlenow considered that, with a regressive lesion, muscle-joint sense recovered more rapidly than cutaneous cinæsthesia but we had the contrary impression when the test of pinch-press discrimination was confined to the back of the hand.

In the initial stages of the investigation we were mainly concerned in comparing the tests of pinch-press discrimination and muscle-joint sense. We had overlooked the fact that, with lesions of the central nervous system, a loss of muscle-joint sense is always accompanied by a loss of two-point discrimination. Head and Thompson (1906) pointed this out and the truth of it appears to be generally accepted although it is not given in standard textbooks of neurology. Our results confirmed this observation and it became apparent to us that the test of two-point discrimination was more sensitive than that of muscle-joint sense.

It appears that the test of two-point discrimination is one which is frequently described but rarely practised. Gowers (1892) and Oppenheim (1911) did not think it had great value and, although Head and his co-workers used it to good effect in their research, their method is not easily applicable to routine clinical practice. The general impression of the test can probably be fairly stated by a quotation from Finlayson (1891). "With every care the results are often unsatisfactory and confusing. In fact considerable intelligence is required in the patients to secure reliable results and they often seem so stupid or careless or fatigued that the results appear a mass of confusion."

On applying the test of two-point discrimination to a series of subjects it was apparent that difficulties often arose in patients who could, on other evidence, be described as poor sensory witnesses and we were thus led to include in our series 10 patients with conditions which were psychological in origin. These patients demonstrated how misleading the test could be.

We concluded that an impairment of two-point discrimination, when it exists as an isolated sensory sign, must either be ignored or interpreted with the greatest caution.

Nevertheless it still seemed important to discover whether two-point or pinch-press discrimination showed the earliest impairment in the presence of an organic lesion. In view of the psychological factors involved a formal investigation could not be planned and it was at length decided to apply the two tests, in addition to the test of muscle-joint sense, to as many patients as possible over a further period of six months. Scoring systems were not used and this afforded the opportunity of comparing the three tests under normal clinical conditions. The results were unequivocal. A loss of muscle-joint sense was always associated with a loss of two-point and pinch-press discrimination. A loss of pinch-press discrimination was always associated with a loss of two-point discrimination. In several patients a loss of pinch-press and two-point discrimination was found in one or more limbs while only the latter was found in other limbs. In a few cases an isolated loss of two-point discrimination was thought to have pathological significance. Our final conclusion was that, ignoring the three exceptions noted in the table of results, the test of two-point discrimination was the most sensitive of the three tests but that in the great majority of patients the test of pinch-press discrimination was the most satisfying and reliable. In practice it emerged that the test of muscle-joint sense could be abandoned in favour of the test of pinch-press discrimination, while dubious results in the latter could, to some extent, be reinforced by the test of two-point discrimination.

Summary

(1) A test is described in which the patient has to discriminate between a pinching and pressing of the skin.

(2) The test was applied to 50 patients and 75 normal controls. When a scoring system is used a clear division can be drawn between normality and abnormality.

(3) The test was compared to the tests of two-point discrimination and muscle-joint sense (perception of direction of passive digit movement).

(4) The tests of two-point and pinch-press discrimination were shown to be more sensitive than the test of muscle-joint sense in the presence of a progressive lesion.

(5) The test of two-point discrimination was thought to be more sensitive than the test of pinch-press discrimination but less reliable.

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BEHAVIOUR OF PYRAMIDAL AXONS FOLLOWING SECTION[1]

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Introduction

Cajal (1928) described the attempt of axons in the white matter of the cord to regenerate following trauma, an attempt which failed after ten to fourteen days, with gradual disappearance of new sprouts, leaving only disconnected "atrophic and monstrous arborizations." More recently some degree of neuronal regeneration has been claimed to occur in the cord of rats by Sugar and Gerard (1940) and in rat, cat and dog by Freeman (1952), a small percentage actually establishing neural continuity across the lesion. Sugar and Gerard considered that the cause of failure in most cases was the rapid growth of glial and connective tissue between the severed cord ends. Brown and McCouch (1947) reported abortive cord regeneration in cat and dog: they found no lack of axonal growth, union being prevented by excessive scar tissue, but the origin of these growing axons, whether from nerve roots or intrinsic cord axons, was not discussed. Davidoff and Ransohoff (1948) prevented access of external connective tissue to the severed cord of the cat by enclosing the stumps in clot-filled gall-bladder or gelatin capsules: in spite of the lack of interference from scarring, no evidence of regenerative power was seen in the transected axons. Barnard and Carpenter (1950) also found in rats that although nerve root fibres invaded scar tissue, intrinsic cord axons showed only a poor attempt at regeneration.

Recently a polysaccharide of bacterial origin, Piromen (Baxter Laboratories) has been described which, among many interesting properties, is reputed to inhibit the growth of glial tissue. Windle and Chambers (1950) reported the growth of axons across the loose tissue scar in the transected cord of Piromen-treated dog and cat, contrasting with the abortive regeneration and dense glial scarring seen in untreated controls. Similarly, growth of peripheral nerve into brain has been

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facilitated by inhibition of scar tissue (Windle, Clemente and Chambers, 1952).

The spinal cord has many complications as a testing ground for regeneration of central nervous tissue. The paraplegic animal is a difficult nursing problem, the histological picture is confused by the profusion of tracts, ascending and descending, and the part played by nerve root fibres, which are known to be virile in their growth, is difficult to assess. It was felt that the medullary pyramid would be more satisfactory for determining this power of regeneration and the importance of the glial barrier in preventing this. The present investigation was designed to ascertain:

(1) The extent to which central ends of pyramidal axons are preserved following section.

(2) Whether these axons exhibit attempts at regeneration.

(3) If so, whether the glial barrier is a factor in preventing regeneration.

(4) The effect of Piromen (Baxter Laboratories) on the formation of such a glial barrier.

Methods

The right pyramid was severed in a series of 12 adult cats with aseptic technique. The animals were anæsthetized by a sodium pentobarbitone solution (1 grain/c.c. Sagatal. May & Baker) 0·5 c.c./kg. intraperitoneally. Atropine 1 mg. (1·0 c.c. of 1/1,000 solution) was then administered by intramuscular injection, the pharynx and larynx sprayed with amethocaine 1 per cent, and a polythene tube inserted into the larynx.

The animal was postured with ventral aspect of head and neck uppermost in a headholder which clamped the canine teeth, bridge of the nose and point of the mandible, allowing clear access to the operative field. Approach to the base of the skull was parapharyngeal: the right longus capitis muscle was reflected from its attachment to the basiocciput, and a window made in the bone with a dental burr. The dura having been cut, a transverse incision was made across the right pyramid with an iridectomy knife. The incision was completed medially with a dural hook inserted under the basilar artery. Post-operative recovery was uneventful apart from some laryngeal stridor in the first twelve hours.

The animals were divided into pairs, one of each pair receiving Piromen (Baxter Laboratories) in the dosage set out below, and one being an untreated control. Pairs were subjected to a terminal experiment after 7, 32, 85, 145, 165 and 173 days. The dosage of Piromen recommended by Baxter Laboratories was 0·6 microgramme/kg. daily by intravenous injection, given in courses of a fortnight, alternating with rest periods of a fortnight. The weight of all cats was in the range 2·2 to 3·0 kg.

during the survival period, so the dosage of Piromen was standardized at 2 microgrammes daily by intravenous injection. These daily injections were given as courses, each of twelve days, interrupted by rest periods of nine days. Activity of the Piromen was checked periodically by taking rectal temperatures before injection, two and four hours after injection; an elevation in temperature of 1-2° F. was usual by comparison with controls.

At the terminal experiment, animals were anæsthetized by Dial (Ciba) 0·5 c.c./kg intraperitoneally. After tracheal cannulation, the basiocciput was bared by removal of larynx, part of pharynx and œsophagus, and reflection of the longi capitis muscles. The pyramids were exposed by burring away the remaining basiocciput and reflection of dura, great care being taken in the separation of adhesions to avoid damage to the pyramids. The electrophysiological activity of the tract was then tested in both normal and operated pyramids, a bipolar stimulating electrode being placed on the pia at the rostral end of the pyramid and recordings taken from the surface of the pyramid at various conduction distances by means of a silver surface macro-electrode. The stimulus, applied to the preparation through a shielded transformer, was a rectangular pulse of 70 volts, 50 microsecs. in duration. The amplified responses were recorded with a cathode ray oscillograph and photographed on to high speed emulsion plates.

At the conclusion of the experiment, the animal was perfused with normal saline, followed by 10 per cent formalin saline, and the medulla removed for histological examination. Transverse sections were taken through the extreme rostral or caudal end of the medulla, and serial longitudinal sections through the operated pyramid. Sections were 10μ in thickness and stained on the slide by a silver technique (Roger's method: modification of Foot).

Results

This series all showed the characteristic "clinical" abnormalities of pyramidotomy during their survival periods. These comprise absence of hopping and placing reactions, deficit in flexion and adduction movements, with abnormal limb postures on the affected side. The animals also displayed a definite contralateral extensor hypertonus more marked in the hind-limb. This resistance to passive flexion was uniform, not of clasp-knife type, and was most obvious when the animal was supported under the thorax and abdomen with limbs hanging freely. The observed changes thus agree with those reported by Marshall (1934), Liddell and Phillips (1944) and, with regard to muscle tone, by Ranson (1936); whereas Tower (1935) considered that there was no true extensor hypertonus.

When the terminal operation was performed, no difference could be observed in the density of adhesions between the Piromen-treated series and controls. The site of the lesion had been varied intentionally, being ventral to the trapezoid body in half the animals and in the middle of the medulla in the remainder. In 7 of the 12 cats the lesion involved the whole width of the pyramid: in the other 5 some medial fibres were spared. The cut involved part of the medial lemniscus or trapezoid body in most cases. The affected pyramid was smaller than its fellow both above and below the scar in cases surviving 85 or more days, the atrophy being more noticeable distal to the lesion (Plate IV, fig. 1).

The pair of animals sacrificed at 7 days showed a similar histological picture; the lesion had been placed some 3 mm. below the trapezoid body in both. All axons distal to the loosely formed and vascular scar were in process of degeneration. Most of them were disrupted into small segments, irregular in contour, staining lightly and thinner than normal. Proximal to the scar degenerative changes of a different nature were present in most axons, and these changes were similar to those described by Cajal (1928) as occurring in the transected spinal cord. The majority of axons appeared larger than normal and stained more heavily, being grossly irregular, some containing a series of bead-like dilatations. Near or in the scar, most fibres terminated in blunt thickened ends resembling sticks, clubs, forks, balls, or rarely in a cystic swelling which seemed to arise within the axon itself. Some axons were seen within the matrix of the scar, but most of these showed signs of degeneration and appeared to be survivors, not pioneers. There were several small networks of thin axons in the scar tissue which had no visible connexion with the residual tract fibres. No unequivocal signs of axonal growth or regeneration such as sprouting from axons or axons curving back in their path, were seen. In the vicinity of the scar and for about a millimetre proximal to it, the area of the tract was studded with small cystic spaces which lay between the axons and pushed them to one side. More rostrally in the medulla where the tract runs ventral to the trapezoid body most of the fibres appeared normal, only some larger fibres showing signs of degeneration.

The two 32-day specimens (both with mid-medullary lesions) showed some difference in the amount of scar tissue, as the control animal had developed a cyst within the scar which was surrounded by a ring of dense glial tissue. However, superficial to this cyst the scar showed no difference from its Piromen-treated companion. In other respects the two animals showed similar changes. Distal to the lesion degeneration of axons was almost complete, only fragments remaining. On the central side, many axons had disappeared in the area close to the scar and the characteristic

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acute change—clubs, retraction balls, etc.—were no longer seen. A number of fibres nearly all of small diameter, persisted to the edge of the scar (fig. 2A, B). As the pyramid was traced rostrally, more large fibres were seen to remain in the tract, until, ventral to the trapezoid body, the constitution of the tract appeared normal (fig. 2c). It thus appeared that large axons had degenerated farther back than the small. Throughout the medulla a profusion of collaterals were given off by pyramidal axons, being made more conspicuous by the degeneration of the medial lemniscus. The small fibres near the scar were normal in appearance but showed no signs of growth into or around the scar. There were few collaterals seen in the scar area, and no reason for the preservation of these axons was noted.

Electrophysiological examination of the tract in the animals before death supports the impression that retrograde degeneration extended more rostrally in the larger fibres. The pyramidal tract contains two groups of fibres which can be demonstrated as two waves of electrical activity (Bishop, Jeremy and Lance, 1953). Fig. 3 (responses a and b) shows the characteristic oscillogram recorded from the normal pyramid at 4 mm. and 7 mm. conduction distance. Fig. 3 (responses c and d) shows the recordings from the affected pyramid at the same conduction distances, the 4 mm. recording being just rostral to the scar and the 7 mm. recording caudal to it. In the former, the first wave is seen to be much smaller than normal and superimposed on a positivity: this is consistent with recording beyond the ends of the remaining large pyramidal fibres, although stimulus artefact is responsible for partly distorting the first wave on both normal and operated sides. The second wave is merely reduced in amplitude, showing that the small fibres, although diminished in number, are conducting up to the recording electrode. The recording at 7 mm. on the affected side shows that no response was obtained from the pyramid distal to the scar.

Cats with survival times of 85 days and more showed complete degeneration of all axons immediately below the pyramidal lesion (fig. 4). There were a few axons some millimetres below the scar seen in longitudinal sections, which could have been preserved ascending pyramidal fibres (Brodal and Walberg, 1952), but the possibility that they were derived from neighbouring tracts or spared corticospinal fibres could not be excluded. The scars were of approximately the same size and density in Piromen-treated cats and controls.

In cases where the lesion was at the distal end of the trapezoid body, some fibres remained on the central side of the scar, resembling the "preserved fibres" of the 32-day specimens. There were no collaterals seen passing to the region of the trapezoid body or other features that

might explain the continued presence of these fibres, and there was no evidence of attempted regeneration. These residual fibres were prominent over the trapezoid body in the 85-day specimens (fig. 5), were less numerous in one of 145 days, and very few in the 165-day cases. In the latter, retrograde degeneration could be seen extending deeply into the pons (fig. 6). Preparations with a lesion placed in the mid-medullary region showed many collaterals passing from surviving axons into the medulla (fig. 7), although the axons were not totally transformed into arciform fibres as Cajal (1928) described in the spinal cord. Some corticobulbar fibres were also seen curving around the caudal border of the trapezoid body. Thus some pyramidal fibres appeared to owe their preservation to the possession of collaterals, whereas others, mostly of smaller calibre, remained on the rostral side of the scar for some months in sites devoid of collaterals.

Discussion

Most of the changes noted here in pyramidal axons following injury have been beautifully described by Cajal (1928) in spinal tracts, including the observation on retrograde axon changes that "the extent of the traumatic degeneration perhaps is in direct relation to the diameter of the axon." There are two important differences from his description in this report.

First, Cajal stated that, although the immense majority of fibres undergo retrograde degeneration and atrophy exclusively, regenerative attempts do occur in some fibres of moderate and small diameter, more marked in young animals. The sprouts are apparent three to four days after the fibres are severed, ramify profusely, and may form an intricate plexus near the scar by six to nine days. This proliferation is arrested at the tenth to fourteenth day and atrophy of new-formed branches commences, being complete by six to eight weeks. In the present investigation there was no indication of any regenerative activity or axonal growth whatever in pyramidal fibres. The behaviour following section of the central ends of pyramidal axons in the adult cat thus appears to be primary retrograde degeneration in most axons, more marked and extending further in those of large diameter, with some of the small fibres remaining near the scar as "preserved axons" showing no regenerative activity.

Secondly, Cajal described the total transformation of axons near the wound after six to eight weeks into arciform fibres which curve into the grey matter. He considered this due to complete atrophy of the portion of every axon distal to its last collateral. This appearance was not observed in the pyramid although many collaterals were present, passing from the residual fibres to the medulla. In addition many small axons persisted in

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areas where there were no obvious collaterals: for example, when the lesion had been placed at the caudal border of the trapezoid body, some axons were preserved in the tract running ventral to the trapezoid body (fig. 5).

The most likely explanation of the above facts is that an injured pyramidal axon promptly degenerates back to the last node of Ranvier. Nodes have been described in the central nervous system by Cajal and others. Recently Hess and Young (1952) investigated nodes of Ranvier in the spinal cord of the rabbit, and found that the internodal length varied from 200 μ in small fibres of 3 μ in diameter to 2,000 μ in fibres of 15 μ diameter. The fibres of the cat pyramid range from 1 to 12 μ in diameter (Brookhart and Morris, 1948) so a similar range in internodal distance would be anticipated. Thus the distance of primary degeneration would usually be greater in a large fibre, and only small fibres would remain in the vicinity of the lesion. Eventually these small fibres gradually degenerate, presumably back to their last collateral, and very few could be seen persisting in the 165 and 173-day specimens (fig. 6). The degree of retrograde degeneration observed in the severed pyramidal tract appears therefore to depend initially on the internodal length of the individual axon, then, over a period of months while the "preserved fibres" are slowly degenerating, on the time that has elapsed since injury: the final extent of degeneration probably depends on the site of the last collateral proximal to the lesion. This hypothesis explains the facts reported here, and also the variability in appearance of retrograde degeneration observed by Tower (1935, 1940), who reported that pyramidal degeneration did not extend centrally beyond the pontine region when the tract was cut in the upper medulla, a fact that she attributed to the presence of pontine collaterals. Lassek (1942) found no changes in the medullary pyramid up to ten months following hemisection of the monkey cord at C_1 segment, and this last observation would suggest that most pyramidal fibres supply collaterals to the medulla.

The study of Holmes and May (1909) appeared to localize the origin of the pyramidal tract to the Betz cells of area 4 by the method of retrograde cell degeneration following hemisection of the cervical cord. It is of interest that the pyramidal tract was examined in one of their human cases, and the amount of degeneration above the cord lesion found to be slight (Howell, quoted by Lassek, 1947). Levin and Bradford (1938) employed the same method in their study of the Macaque cortex, and found that a total of 31,000 cells (including both hemispheres) degenerated following cervical hemisection. As there are 554,000 fibres in the Macaque pyramid (Lassek, 1941) less than 5 per cent can be traced to their cells of

origin by retrograde cell changes. Lassek (1942) considers that the affected cells may not degenerate completely and remain although reduced in size. However, as Walshe (1942) points out, neuronophagia was observed by Holmes and May, and it seems more likely that these cells do degenerate completely. If so, it is probable that the axons of the cells that undergo complete retrograde degeneration supply no collaterals to supraspinal regions.

Brodal and Walberg (1952) reported that about 4 per cent of pyramidal fibres degenerate on the central side of cord lesions in the cat; these degenerating fibres were traced to pontine nuclei and cortex, and some degenerating boutons found in these sites. There is thus good evidence that the pyramidal tract contains ascending fibres. However, the possibility that some descending pyramidal fibres undergo complete retrograde degeneration back to the cortex cannot be excluded. Brodal and Walberg quote as decisive the experiment of Lassek (1942) who failed to find evidence of degeneration in the pyramid up to ten months after hemisection of the monkey cord at C_1; but the experiment could equally be considered to show that there are no ascending fibres in the tract. It merely emphasizes the difficulty in observing the loss of a small number of fibres from a tract in chronic studies.

The administration of Piromen (Baxter Laboratories) during survival periods did not appear to alter the size or quality of the glial scar in the pyramids. This finding was unexpected in view of reports that glial growth was inhibited in animals under treatment with this bacterial pyrogen (Windle and Chambers, 1950; Windle, Clemente and Chambers, 1952). These workers have demonstrated histologically neurons traversing the site of the lesion in Piromen-treated animals with transected cords, and have obtained electrophysiological signs of activity from these regenerating neurons (Windle, Clemente, Scott and Chambers, 1952). The Piromen used in the present series retained pyrogenic properties throughout the survival period; it is possible that glial inhibition may depend on some factor which may deteriorate independently of this. In view of the small numbers in the present series, which was limited by the supply of Piromen available, further reports from other sources will be of interest.

The lack of regenerative attempt in pyramidal axons parallels the findings of Davidoff and Ransohoff (1948) and Barnard and Carpenter (1950) in spinal cord studies. However, some authors have demonstrated that such attempts can occur in the cord. Many factors have been shown to influence cord regeneration, such as the age of the animal, blood supply to the cord stumps (Sugar and Gerard, 1940), type of cord lesion and general metabolic state of the animal (Freeman, 1952). There may also be individual differ-

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ences in regenerative ability from tract to tract, and even between neighbouring axons in the same tract. Peripheral nerve regenerates quickest when the lesion is close to the parent cell body, and the rate of growth becomes slower as the axon grows away from it (Sunderland, 1950). If a similar relationship holds in the central nervous system, regeneration would be expected to occur most readily in axons which have been severed in proximity to the cell body. In spinal cord lesions there would always be a large number of propriospinal neurons in which the cut is close to the cell body, in addition to nerve root fibres whose virile growth propensities are well known. Pyramidal tract fibres whether in medulla or cord are far from their cell body and their lack of regenerative power might be thus explained.

Summary

(1) Unilateral section of the pyramidal tract in the medulla was performed in 12 adult cats, and the condition of the affected tract was examined electrophysiologically and histologically after survival periods of up to 170 days. 6 cats were treated during this time with Piromen (Baxter Laboratories), a pyrogenic agent reported to inhibit glial tissue and thereby promote axonal regeneration in the central nervous system.

(2) No attempt at regeneration was observed in pyramidal axons. Complete degeneration occurred in almost all axons distal to the lesion although a few axons remained in the caudal part of the pyramid. Axons on the central side of the lesion underwent a variable degree of retrograde atrophy. This degeneration was more marked in large axons, some small axons persisting to the edge of the scar for some months. Although the pyramidal tract gives off many collaterals in pons and medulla, this did not appear to be the only factor in maintaining persisting axons. It is postulated that the axon degenerates back to a node of Ranvier within some weeks of injury, and subsequently, after some months, back to the last collateral.

(3) The size and quality of the glial scar were not affected by the administration of Piromen during post-operative life. However, the glial barrier did not appear to be a factor in preventing the growth of axons as no attempts at growth were observed.

Acknowledgments

I wish to thank Mr. G. Hayden who prepared all the histological sections, and Mr. Woodward Smith and Mr. K. Clifford of the Department of Illustration, University of Sydney, for the photomicrographs. Baxter Laboratories (Illinois) very kindly provided the Piromen used in this investigation.

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PLATES IV, V and VI

LEGENDS FOR FIGURES 1—7

FIG. 1.—Medullæ from cats killed 173 and 85 days respectively after pyramidal section. Both cats were treated with Piromen during post-operative life. The scars, indicated by arrows, are placed at the lower border of the trapezoid body. The affected pyramid is atrophied above and below the lesion in both cases.

FIG. 2.—A, Longitudinal section through the medulla in Piromen-treated cat sacrificed at 32 days. Pyramidal fibres can be seen lying horizontal in the section, superficial to the trapezoid body at c and in the vicinity of the scar (arrow) at b. B, High-power field from above section at point marked b. Fibres are sparse near the scar and predominantly of fine calibre. A collateral can be seen springing from one axon in the upper left quadrant. C, High-power field from the same section, point c. The tract over the trapezoid body contains many fibres of large calibre. Comparing b and c, both at the same magnification, it can be seen that larger fibres degenerate farther back from the scar than the smaller. All sections illustrated are silver-stained (Roger's method: modification of Foot).

FIG. 3.—Oscillographic records obtained before death from the pyramids of a 32-day cat. a and b show the two characteristic waves of pyramidal activity recorded from the normal pyramid at 4 mm. and 7 mm. respectively. c and d are the corresponding responses from the operated pyramid (the histology of which is shown in fig. 2), c being recorded just proximal to the scar (4 mm. conduction), and d distal to it (7 mm. conduction). The stimulating electrode was placed at the extreme rostral end of the pyramid on both normal and operated sides. Both waves of activity are

smaller in response c than a and the faster wave is superimposed on a positive deflection because the recording electrode is distal to the termination of the larger fibres, although some distortion is due to stimulus artefact. Record d shows that there is no electrical activity distal to the scar. Time marker, 0·2 msec. intervals.

FIG. 4.—*a*, Transverse section through the lower end of the medulla in 85-day control animal below the lesion. The affected pyramid is slightly atrophied and stains more lightly than the normal side. B, High-power field from atrophied pyramid. Part of an arcuate fibre lies horizontally in the field. All pyramidal fibres appear to have degenerated, but in a transverse section it is difficult to determine whether or not any axons remain; however, in longitudinal sections a few fibres can usually be seen in the caudal part of the atrophied pyramid. *c*, Normal pyramid. Same magnification as *b*.

FIG. 5.—Longitudinal section showing fibres remaining over the trapezoid body proximal to the scar in 85-day control animal. The scar is seen to involve the whole width of the pyramid and to extend into the trapezoid body in the direction of the arrow. Many fibres, mainly small, persist to the edge of the scar. Piromen-treated cats presented similar histological pictures to the control animals illustrated in figs. 5, 6 and 7.

FIG. 6.—Longitudinal section showing retrograde degeneration extending into the pons (PO) in 165-day control cat. Few fibres now remain in this part of the pyramid (PY), but as the pyramidal bundles are traced rostrally into the pons, they contain a steadily increasing number of fibres until their constitution appears normal in the upper pons. TB, trapezoid body.

FIG. 7.—Longitudinal section through upper medulla in 147-day control animal. The trapezoid body is seen on the right of the photomicrograph, and the scar (arrow) on the left. The fibres remaining in the pyramid superficial to the trapezoid body at this survival time appear to be either corticobulbar fibres or corticospinal fibres which have atrophied distal to a collateral. The latter is suggested by those fibres which can be seen turning abruptly to plunge into the medulla.

PLATE IV

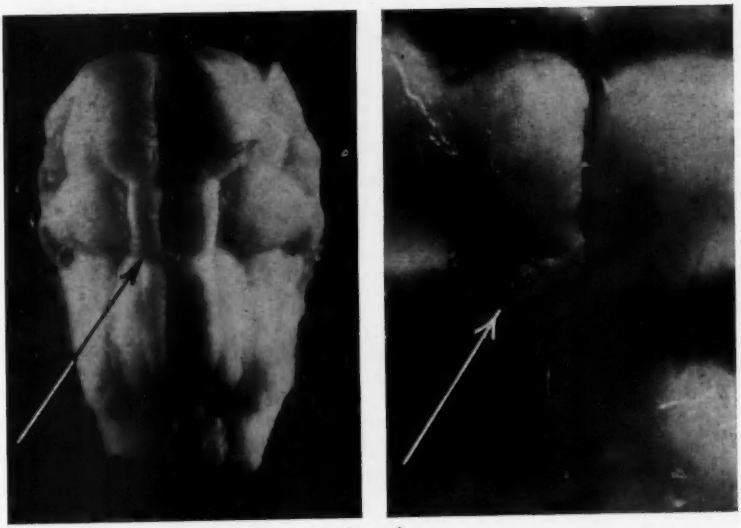

FIG. 1

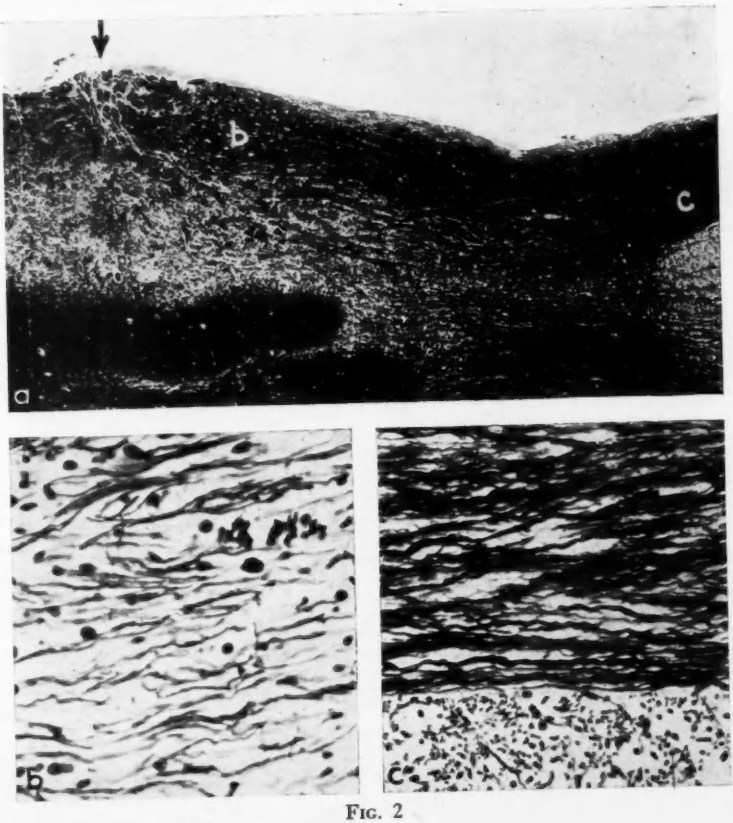

FIG. 2

To illustrate article by J. W. Lance

PLATE V

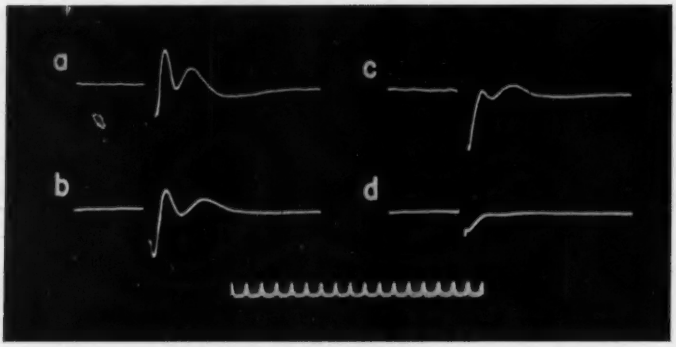

FIG. 3

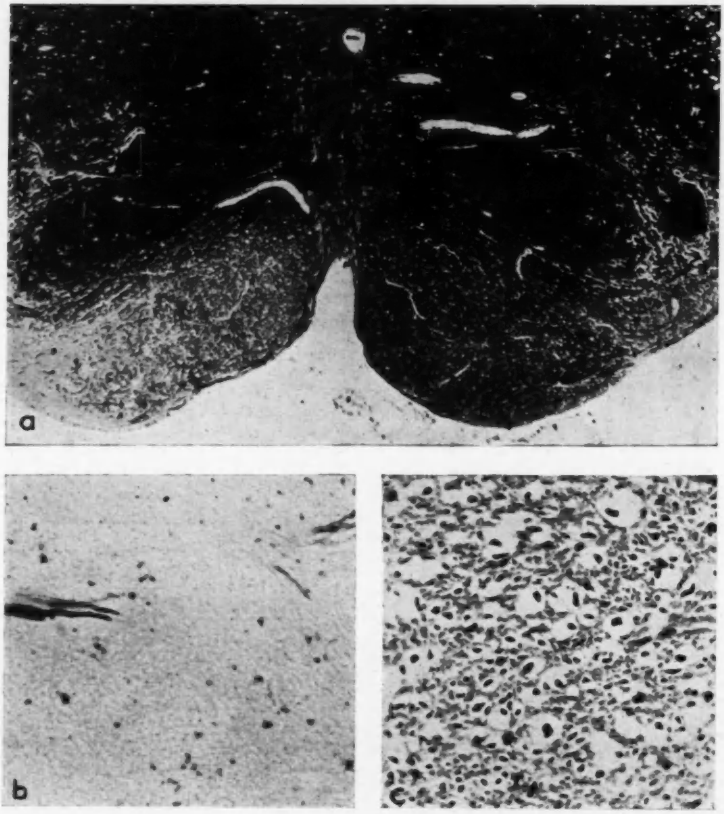

FIG. 4

To illustrate article by J. W. Lance

PLATE VI

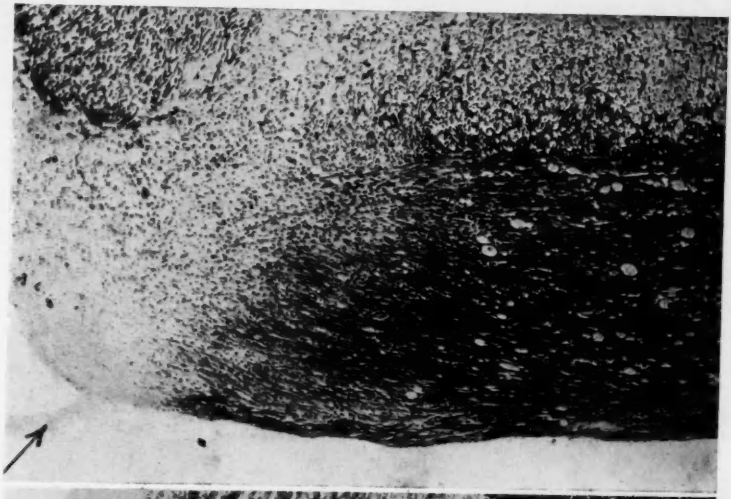

FIG. 5

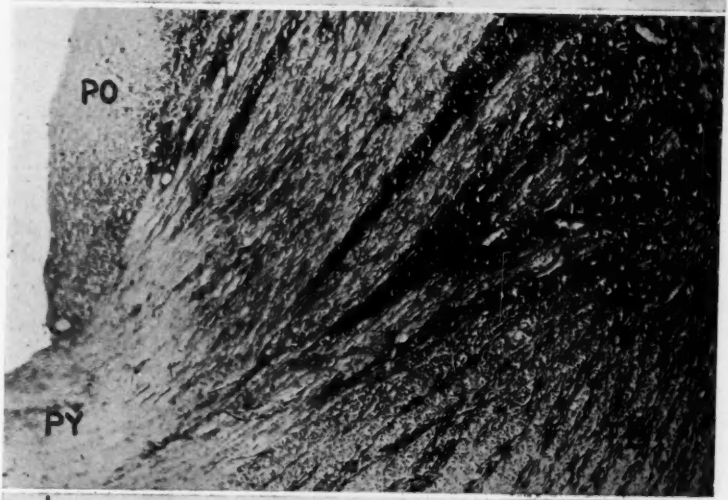

FIG. 6

FIG. 7

To illustrate article by J. W. Lance

TEMPORAL DISPERSION IN CORTICAL AFFERENT VOLLEYS AS A FACTOR IN PERCEPTION, AN EVOKED POTENTIAL STUDY OF DEEP SOMATIC SENSIBILITY IN THE MONKEY

BY

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THE concept that somatotopic representation of body regions in the sensory cortex provides the basis for localization of peripheral stimuli receives support from both cortical stimulation in humans (Penfield and Rasmussen, 1950) and from evoked potential studies in animals (Adrian, 1941; Woolsey and Fairman, 1946). Nevertheless the well-known spatial overlap in cortical representation (Marshall, Woolsey and Bard, 1941) and the evidence for bilateral representation of deep somatic structures in the first somatic area (Mickle and Ades, 1952) indicate that some factor other than mere spatial dispersion of impulses is involved in conscious sensory localization. In the first somatic area of the marsupial phalanger and of the rabbit the ipsilateral representation of each limb occupies an area concentric within, and in most cases only slightly smaller than the contralateral representation (Adey and Kerr, 1953).

Lashley (1951) has pointed out that integration ascribed to the spatial distribution of excitations in the nervous system has been much more intensively studied than temporal aspects of nervous activity, and that theories of integration are based almost exclusively on space properties.

More recently, Adey, Carter and Porter (1953) have observed that afferent volleys from deep structures in homolateral and contralateral limbs show constant, but clearly different patterns of temporal dispersion in the cortex of the first somatic area. Although the total responsive zone remained constant in size and disposition during stimulation of widely separated points in the contralateral forelimbs and digits, the cortical point of most rapid response showed constant alteration in position with alteration in the site of peripheral stimulation. The latency decreased rapidly from the periphery to the centre of the cortical area concerned. It was suggested therefore that localization may be determined by the

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point of shortest latency within an activated area of essentially constant site and dimensions.

No studies of the extent of the cortical representation of deep somatic sensibility have so far been reported in the primate, although Malis, Pribram and Kruger (1953) have observed that stimulation of the sciatic nerve in the monkey evokes potentials in an area of cortex considerably larger than the tactile representation of the lower limb as recorded by Woolsey, Marshall and Bard (1942). The present investigation has aimed at determining the approximate extent of face, forelimb and hindlimb representations of certain forms of deep somatic sensibility in the first somatic area. In view of the considerable spatial overlap which we have observed in these representations, particular attention has been directed to the temporal dispersion of the afferent cortical volleys throughout each responsive zone.

Material and Methods

Five rhesus monkeys (*Macacus rhesus*) have been used in this investigation. Anæsthesia was induced by intraperitoneal injection of veterinary Nembutal solution in an initial dose of 0·5 c.c. per kg. body-weight, supplemented by maintenance doses as required. The evoked potentials were augmented by the administration of chloralose in doses of 7–10 mg. per kg. body-weight per hour, after the method of Woolsey and Fairman (1946).

Tracheotomy was performed at the commencement of each experiment and artificial respiration instituted, although spontaneous respiration was rarely so depressed as to make this a necessity. The major part of the dorsolateral aspect of the hemisphere was exposed by removal of a bone flap. The dura mater was carefully preserved at this stage and the skin edges approximated with Michelle clips. After an interval of three to four hours, during which a uniform depth of anæsthesia was maintained, the brain was re-exposed and the dura mater removed. The exposed surface of the hemisphere was bathed in mineral oil at 37° C. The oil was changed once per minute throughout the experiment. The room temperature was maintained at 28–33° C. throughout the experiment, which, in some instances, lasted over twenty-four hours. In the longer experiments, saline and dextrose were administered at intervals through a gastric tube.

The head was retained in a stereotaxic instrument. The recording electrode was a tapered nichrome wire and the rounded tip in contact with the cortex had a diameter of approximately 0·25 mm. The neutral electrode was a similar piece of wire inserted under the skin of the neck or forehead. The action potentials were amplified in a resistance-capacity coupled amplifier with a uniform frequency response from 1 cycle to 10 kilocycles per second.

In all experiments skin incisions were made at the site of stimulation. All cutaneous tissues were well cleared to expose an area of muscle or periarticular structures in the floor of the incision, which was bathed in mineral oil. Incisions were made on the flexor aspect of the distal forearm and on the lateral aspect of the hindlimbs just above the ankle. In the hand, additional incisions extended along the radial border of the first digit and along the ulnar border of the third and fifth digits. Similarly in the face, incisions were made in the upper eyelid, in the upper part of the cheek lateral to the nasal furrow, and in the vicinity of the lower lip. Stimuli were delivered once per second to the subcutaneous structures so exposed with bipolar electrodes having a variable tip separation of 1–10 mm. Square wave

stimuli of 0·1 msec. duration and an amplitude of 1–10 volts were obtained from a generator triggered from the cathode-ray sweep (Attree, 1950) and applied through an electrostatically shielded pulse transformer.

In each experiment the deep tissues exposed in the incisions were stimulated and a survey made of the total cortical area responsive to stimulation at these fixed points. In the early experiments, coronal and sagittal planes were selected from this map, such that they intersected in the region of maximal response. Photographic records were then made in 1 mm. steps along these intersecting planes across the entire responsive area. In later experiments photographic records were prepared in 2 mm. steps over the entire responsive area. Although the measurement of temporal dispersion in the afferent volleys may be complicated in the latter method of recording by the longer time elapsing in the mapping of a single representation (with possible alteration in depth of anæsthesia) there is no evidence that this significantly modifies the results.

The form of the evoked potentials has been described in detail elsewhere (Adey and Kerr, 1953) and agrees well with that noted by other workers. They show an initial surface-positive phase succeeded by a surface-negative wave, the latter disappearing in deep anæsthesia.

Observations

As had been noted earlier in stimulation of the prehensile forepaw of the marsupial phalanger (Adey and Kerr, 1953) the total area of responsive cortex was approximately the same from stimulation of such widely separated points of a particular part as the front and back of the wrist, and the first and fifth digits. Evidence will be presented below for the existence of an ipsilateral representation in the same responsive area.

Within each responsive "field" or "pool," significant variations in latency of the responses to contralateral stimulation were observed. The latency of the responses was measured from the shock artefact to the inflexion of the initial surface-positive wave. With contralateral stimulation, the latency at the centre of the responsive area was considerably shorter than at the periphery and varied by not more than 1 msec. over many minutes, with a slightly larger variation at the periphery. Although a general relationship was noted between the amplitude of the surface-positive wave and the shortness of the latency, the amplitude of this wave was much more labile than its latency, particularly with the return of spontaneous trains of thalamocortical waves in lighter anæsthesia. Latency of contralateral responses did not appear to alter significantly with changing planes of anæsthesia.

(1) *General arrangement of body regions on the cortical surface.*

Three basic subdivisions could readily be distinguished, corresponding to face, arm and leg representations. Each of these fields formed a continuous sheet of responsive cortex, and while the areas so mapped extended considerably beyond the accepted confines of what is currently regarded as "sensory" cortex, each such region appeared to possess definite

boundaries which were constant in a particular experiment and showed a close correlation in different animals. Since the initial surface-positive deflection of even the marginal responses occurred within 20 msec. of the stimulus, and since the cortex was continuously responsive from the central zone at the fissure of Rolando to the margins of the area, it would appear reasonable to regard the whole area as primary sensory cortex.

It will be seen (fig. 1) that the three divisions of the trigeminal nerve jointly formed a face representation reaching anteriorly for a short

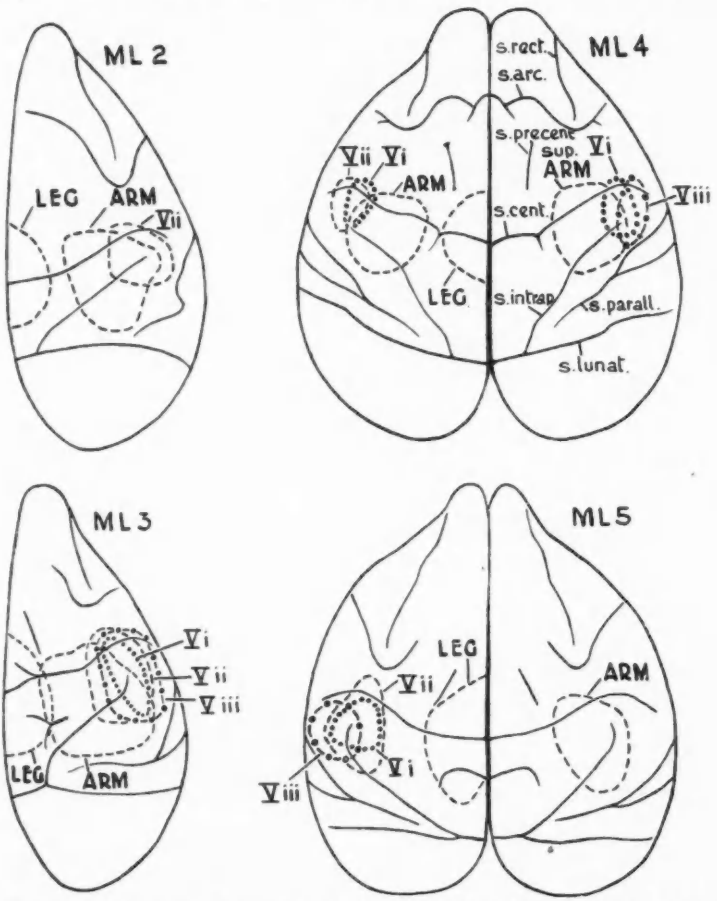

FIG. 1.—Scale drawings prepared from stereotaxic maps showing the extent of the responsive cortex to deep stimulation. Particular care has been taken in these maps to preserve the true relative sizes of each responsive field, thus avoiding foreshortening of the face and arm representations.

(*For abbreviations on figs. see page* 343)

distance in front of the central sulcus. There was considerable overlap in the spatial representation of the divisions of the trigeminal nerve. Stimulation in regions innervated by the mandibular and maxillary divisions evoked potentials in two areas which were coincident except for small strips above and below. The ophthalmic division was represented in a much smaller area totally enclosed within the overlapping maxillary and mandibular areas.

The arm representation was larger than the face area, which it overlapped appreciably antero-inferiorly. There was a significant part of the arm representation in the precentral region. The separate stimulation of deep tissues of the first, third and fifth digits and the flexor aspect of the distal forearm evoked potentials throughout this area without significant modification in its boundaries.

The leg area extended to within a few millimetres of the arm representation and overlapped it in one experiment. Anteriorly it included a large segment of the precentral cortex. The responses adjacent to the medial margin of the hemisphere were small. The cortex of the medial aspect has not been examined.

(2) *Temporal dispersion of cortical afferent volleys in the arm area; initial observations.*

Since the separate stimulation of the digits of the hand evoked potentials in a "field" or "pool" of essentially constant site and size, it appeared unlikely that the spatial dispersion of impulses on the cortical surface would *per se* provide an adequate explanation for the physiological phenomena of perception. An attempt was therefore made to determine any constant patterns of temporal dispersion in the afferent volleys arriving in the responsive field.

In comparison with similar investigations in the lissencephalic brains of the rabbit and marsupial phalanger, this proved considerably more difficult, since in the monkey much of the sensory cortex lies buried in the central and intraparietal sulci. Initially, plots of responses were made along coronal and sagittal planes which intersected in the centre of the postcentral gyrus. These plots failed to disclose the sharply decreasing central latency seen in the rabbit and phalanger (Adey, Carter and Porter, 1953), and were then supplemented by the following investigations.

(*a*) *Latency plots made along the posterior lip of the central sulcus* (fig. 2).—It will be seen that the most rapid responses from the thumb appeared 2–3 mm. from the lower end of the responsive area, with the latency decreasing from 14 msec. superiorly to a minimum of slightly less than 5 msec. and thence increasing to 8 msec. at the lower end of the

plot. On the other hand, when responses from the third and fifth digits were similarly mapped, the responses with shortest latency appeared about 4 mm. higher on the central sulcus. The latency curves for each of these digits decreased from 12–16 msec. peripherally to 7–8 msec. centrally. Although the points of shortest latency for the third and fifth digits were clearly separated from the corresponding point for the thumb, a plot made in this way did not disclose separate representations for the third and fifth digits.

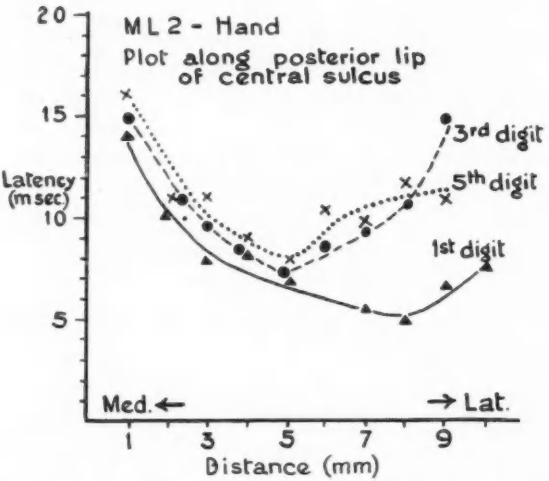

FIG. 2.—Plots of latencies of potentials evoked by stimulation of digits of contralateral hand, and recorded along the posterior lip of the central sulcus.

It became apparent from these initial latency mappings that linear plots, even in carefully selected planes, were unlikely to give a clear picture of the temporal dispersion of impulses arriving at the surface of such a large responsive area. Moreover, a significant portion of the total responsive field obviously lay buried in the depths of the central and intraparietal sulci (fig. 7). It was therefore decided to examine the latencies of responses in portions of the buried cortex, particularly in regions where surface mappings suggested that further decreases in latency might be found.

(*b*) *Latency of forelimb responses recorded from the posterior bank of the central sulcus.*—After mapping responses in front and behind the central sulcus from stimulation of the digits and distal forearm, the pia mater was incised anterior to the central sulcus and by careful suction the precentral gyrus was removed to expose the cortex on the posterior wall of the sulcus. The exposure extended almost the whole length of the

sulcus and post-mortem examination confirmed that, except adjacent to the floor of the sulcus, the pia mater on the posterior wall was undamaged (fig. 7A). The cortex of the postcentral gyrus appeared fully responsive half an hour after the ablation.

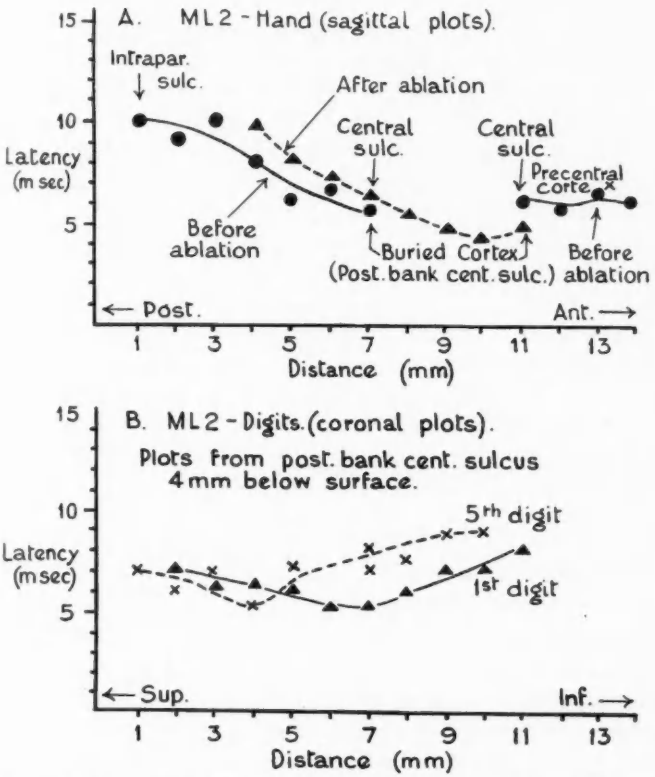

FIG. 3.—A. Plots of latencies of responses from stimulation at contralateral wrist mapped sagittally across the central sulcus (solid line) and in the posterior bank of the central sulcus after removal of precentral cortex (dashed line).

B. Records from the posterior bank of the central sulcus from stimulation of digits of opposite hand.

Prior to the removal of the precentral cortex distal forearm responses mapped sagittally showed a progressive decrease in latency from 10 msec. posteriorly at the intraparietal sulcus to 6 msec. at the posterior lip of the central sulcus. Farther forward, the latency varied slightly between 6 and 7 msec. to the anterior limit of the responses (fig. 3A). After removal of the precentral gyrus the mapping in a sagittal plane was

repeated. It will be seen that the disturbance inevitably associated with the ablation did not significantly modify the latency of the forearm responses from the free surface of the gyrus. When the recording was extended to the buried cortex on the posterior bank of the central sulcus, there was a further reduction in latency to between 4 and 5 msec. at the deepest point examined 4 mm. from the surface of the gyrus.

The latency of responses from the separate stimulation of the first and fifth digits was also recorded from the entire length of the exposed posterior bank of the central sulcus at a depth of 4 mm. from the surface (fig. 3B). These responses were smaller than those nearer the free surface of the gyrus, and at some points there was difficulty in the precise determination of the inflexion from latency measurements. With latencies so short even small errors may significantly modify the resulting curves. Both curves showed a central decrease in latency, with the point of shortest latency for the fifth digit lying medial to that for the thumb, although the shallow slope of the two curves did not allow a sharp separation.

Although these measurements suggested significant gradients of latency across the responsive area, with the most rapid responses appearing in the vicinity of the central sulcus, additional information on the temporal dispersion of afferent impulses was sought from latency maps of all the exposed cortex in face, arm and leg areas.

(3) *Latency records mapped over the whole responsive area of exposed cortex.*

(*a*) *The forelimb area.*—The following exploration was performed in five hemispheres in three monkeys. The flexor aspect of the distal forearm was stimulated and the exposed cortex examined in 2 mm. steps, thus defining the limits of the arm "field." The thumb, middle and little fingers were then separately stimulated and a complete set of photographic records of the evoked potentials prepared for each digit in 2 mm. steps over the whole area. Two or three cathode-ray traces were usually recorded at each point.

A small zone was thus found for each digit in the vicinity of the central sulcus where afferent impulses arrived perceptibly earlier than in any other part of the responsive surface cortex. The latency of these most rapid responses lay in the range 5–9 msec. for each digit. The latency in surrounding areas increased to 12–14 msec. in the space of a few millimetres. When these regions of early responses were compared on a single map, they fell into a characteristic pattern in all experiments (figs. 4 and 5), the thumb region lying near the lower end of the active area, the middle finger region about 3 mm. higher and the little finger zone near the upper

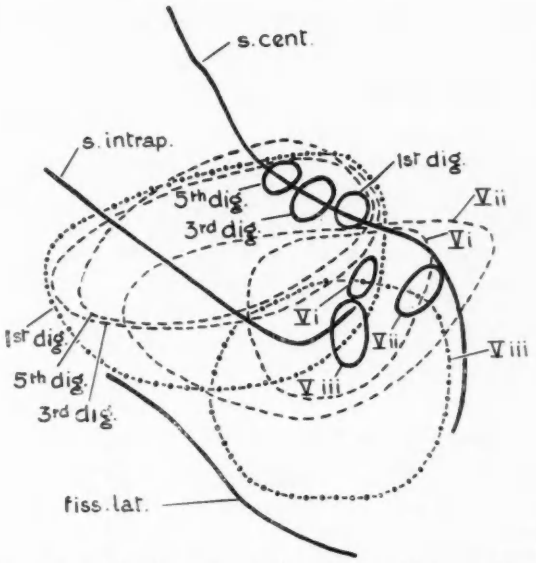

FIG. 4.—Responsive fields from stimulation of first, third and fifth digits of the hand and from regions of supply of each division of the trigeminal nerve. In each case short latency zones indicated in solid outline and total responsive field in interrupted outline.

border of the responsive area. It is of interest that the shortest latency potentials following stimulation of the ophthalmic division of the trigeminal nerve appeared about 4 mm. inferior to the short latency zone for the thumb and lay in the region of overlap of the face and arm areas.

(*b*) *The face area.*—Latencies were measured over the whole responsive area from the separate stimulation of regions supplied by each division of the trigeminal nerve. Much of the cortex of the face area lies buried in the central sulcus and in the lower end of the intraparietal sulcus. Latency gradients in this free cortex tended to be smaller than in the forelimb field. As has been noted previously (Woolsey, Marshall and Bard, 1942) the spatial pattern of the face representation showed more variability in different animals than did the forelimb field.

On stimulation of the tissues of the upper eyelid, the most rapid responses were seen with a latency of 5 msec. in a region extending forward and slightly upward from the lower end of the intraparietal sulcus towards the central sulcus. The evoked potentials in surrounding regions appeared with a latency of 7–9 msec. Although in different experiments this short latency zone occurred in varying relationship to the sulci, it was found to lie between corresponding zones for the thumb superiorly and the

maxillary trigeminal representation inferiorly in all four hemispheres examined.

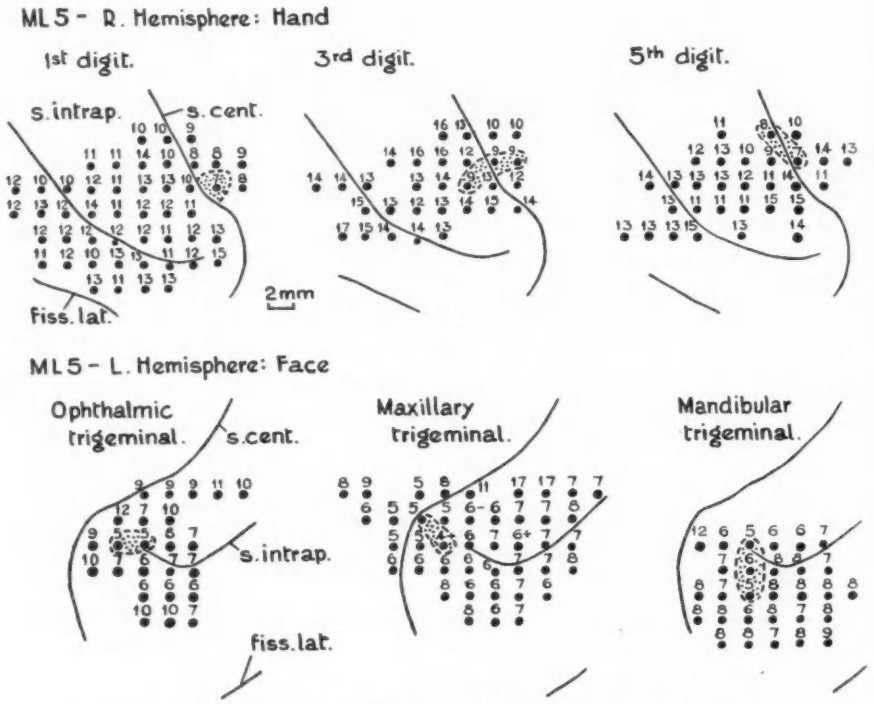

FIG. 5.—Latencies in milliseconds recorded in 2 mm. steps over the entire responsive field for each digit of the hand, and for the face. Short latency zones indicated by dashed outline.

The most rapid cortical responses from stimulation of deep tissues in the area of supply of the maxillary division of the trigeminal nerve appeared with a latency slightly less than 5 msec. adjacent to the central fissure in a zone lying antero-inferior to the corresponding ophthalmic trigeminal zone. The short latency mandibular trigeminal potentials, evoked by stimulation of the lower lip, appeared in an arc of cortex surrounding the lower end of the intraparietal sulcus (figs. 4 and 5).

(*c*) *The hindlimb area.*—Although the extent of the hindlimb area was mapped in four hemispheres, a complete latency map of the surface cortex was plotted in only one (fig. 6). The exposed surface of muscles on the lateral aspect of the distal third of the leg was stimulated. The most rapid responses then appeared along the superior postcentral sulcus, with

a latency of 11 msec. This short latency zone lies near the posterior border of the responsive field, with latencies increasing to more than 18 msec. peripherally.

(4) *Extent of ipsilateral responses.*

Our studies in the monkey of responses in the ipsilateral hemisphere to stimulation of the fore- and hindlimbs have not been as extensive as those in the rabbit and marsupial phalanger reported elsewhere (Adey and Kerr, 1953; Adey, Carter and Porter, 1953). Sufficient data are available for the monkey, however, to support the findings in lower mammals of an ipsilateral representation of the limbs in the first somatic area. It was found that with stimulus repetition rates in excess of one per second the ipsilateral responses fatigued rapidly and disappeared entirely after the first few stimuli. With a stimulus interval of 2 seconds, the responses were much more constant, but still tended to disappear in deep anæsthesia.

(*a*) *Ipsilateral forelimb responses* (fig. 6 and Plate VII, fig. 2).—The deep tissues of the flexor aspect of the ipsilateral forearm were stimulated just above the wrist. The responses appeared in an area with the same general

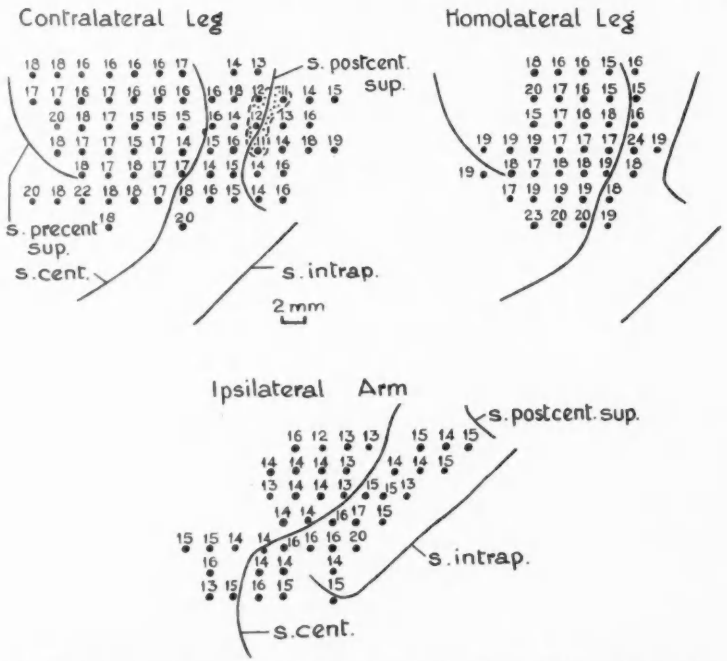

FIG. 6.—Latencies in milliseconds recorded in 2 mm. steps from stimulation of contralateral and ipsilateral legs and from the ipsilateral arm.

contours as that for contralateral stimulation, except posteriorly where they were found only in the anterior half of the postcentral gyrus. The evoked potentials were most constant in form in the cortex adjacent to the anterior and posterior banks of the central sulcus. They were characterized by an initial surface-positivity lasting 20–30 msec. The ensuing surface-negative wave varied greatly in size with successive stimuli. The latency of these potentials lay in the range 13–17 msec. over the whole responsive area without a zone of constant shortening in any part of the exposed cortex. The largest responses were recorded adjacent to the central sulcus and decreased progressively towards the periphery.

(*b*) *Ipsilateral hindlimb responses* (fig. 6 and Plate VII, fig. 3).—From stimulation of deep tissues on the lateral aspect of the distal third of the leg, potentials were evoked in an area concentric with that yielding contralateral leg responses. Its extent coronally corresponded closely with the contralateral leg area. Sagittally, however, responses were limited in the postcentral region to a narrow rim of cortex adjacent to the central sulcus. Anteriorly they did not extend as far forward as the contralateral responses. The ipsilateral responses on the exposed cortex had a latency of 16–20 msec. without a zone of significant shortening. As in the arm area these potentials showed an initial surface positivity lasting 20–30 msec.

(5) *Mode of activation of the responsive cortex.*

It seemed from latency records that, for each site of peripheral stimulation, contralateral responses appeared in an area containing a central zone where afferent volleys could be first detected, surrounded by regions in which the evoked potentials appeared progressively later. Although complete examination of buried cortex was not possible, this area apparently formed a continuous sheet of responsive cortex. However, it was not clear from these experiments how activity spread to the peripheral parts of the area, whether by primary temporal dispersion in thalamo-cortical paths or by secondary activation of cortico-cortical paths radiating from a small primary responsive area.

Evidence will be presented from three experiments involving restricted cortical ablations which suggests that in part at least the peripheral responses are conveyed through cortico-cortical paths from a central primary responsive zone. It must be stressed that the interpretation of data drawn from this type of experiment is particularly difficult where, as in the present case, the inferences to be drawn are based partly on the disappearance of responses after the cortical excision. It is apparent that this type of interference is at best a crude procedure, and the persistence of responses in adjacent cortex is certainly more remarkable than their disappearance. In each case the extent of the lesion has been checked histologically.

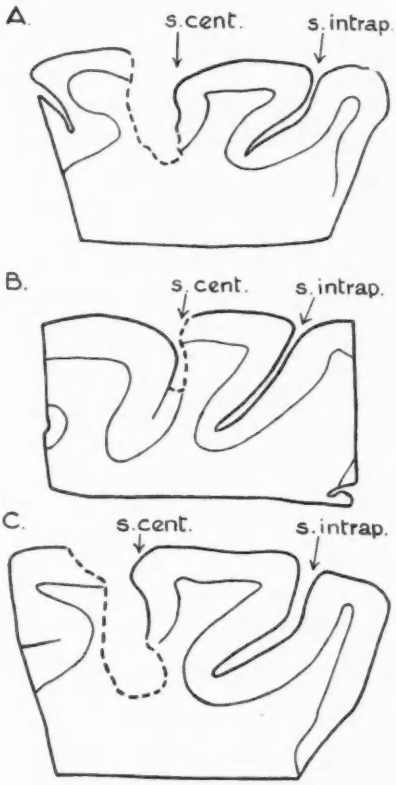

FIG. 7.—Extent of cortical ablations (indicated by dashed outline) in three experiments described in text. Prepared from camera lucida drawings at same magnification in each case.

(*a*) *Effects of ablation of precentral cortex* (fig. 7A).—The cortex on the anterior bank of the central sulcus was carefully sucked out in an ablation running the whole length of the arm field in an immature macaque. The lesion also removed the postcentral cortex at the deepest part of the sulcus, but did not significantly involve the underlying white matter. No significant alteration in the size of the responsive postcentral region was noted, and careful mapping of the latencies of the postcentral responses showed no significant variation from those mapped preoperatively (fig. 3A).

(*b*) *Effects of limited resection of postcentral cortex* (fig. 7B).—Here the cortical removal was confined to a narrow strip about 2 mm. wide extending along the whole length of the arm representation in the region adjacent to the posterior bank of the central sulcus. The ablation extended to a

depth of 6 mm. or a little more than half the total depth of the sulcus. Responses were recorded subsequently from the free surface of the precentral gyrus, and also from free postcentral cortex in front and behind the intraparietal sulcus. The latencies of these responses were in the range 8–12 msec. and resembled closely those recorded before the ablation.

(c) *Effects of combined precentral and postcentral ablation* (fig. 7c).—Here all precentral cortex lying in the central fissure was removed throughout the length of the arm representation. The lesion also removed all postcentral cortex in the deeper half of the central sulcus and extended appreciably into the white matter at the narrow neck of the gyrus. No arm responses could be recorded subsequently from any part of the previously responsive arm area, including the more posterior regions adjacent to the intraparietal sulcus. The cortex behind the intraparietal sulcus had previously been responsive and its subjacent white matter was not involved in the lesion.

It may be suggested from these relatively crude experiments that the cortex lying behind the intraparietal sulcus was excited by a cortico-cortical relay arising from a central responsive region in the vicinity of the central fissure. It is here also that the cortical afferent volleys have been shown to arrive with the shortest latency. However, responses with appreciably longer latency persist in the nearby cortex on the free surface of the postcentral gyrus after extensive resection of this short latency zone on the posterior bank of the central sulcus (fig. 7B). This suggests but does not prove that the cortex in the immediate vicinity of the short latency zone may be activated by a primary thalamo-cortical volley showing a significant degree of temporal dispersion.

Discussion

Stimulation of deep tissues in the monkey evokes responses which show the same basic spatial arrangement of body regions on the cortical surface as seen with tactile stimulation (Adrian, 1941; Woolsey, Marshall and Bard, 1942). The three major "fields" or "pools" in the main sensory strip respond to stimulation of the face, arm and leg respectively. However, the cortex responsive to deep stimulation appears more extensive than that to tactile stimulation, for it extends from the region of the central sulcus as a continuously responsive sheet into the precentral region and posteriorly into the so-called "parietal association" cortex. Mountcastle, Covian and Harrison (1952) have shown that in the cat the responsive area from deep stimulation extends appreciably beyond the corresponding tactile representation.

Our findings confirm the extent of the precentral hindlimb represen-

tation recently reported in the monkey by Malis, Pribram and Kruger (1953) from stimulation of the sciatic nerve. The precentral representation is less extensive in the arm area than in the leg, and in the face region precentral responses were not usually extensive. Human subjective responses to electrical stimulation extend farther into the precentral cortex in the arm area than in either the leg or face representations (Penfield and Rasmussen, 1950).

In many respects our map from deep stimulation in the monkey resembles that of Dusser de Barenne (1924) from strychnine studies. Later studies by Dusser de Barenne and McCulloch (1938) have confirmed the functional extension of the sensory cortex into the precentral region and posteriorly into cortex behind the intraparietal sulcus. Their studies and the more recent work of Malis, Pribram and Kruger (1953) suggest that the precentral representation exists independently of the postcentral representation. Our studies in the arm area suggest that the afferent volleys arrive first in the cortex adjacent to both banks of the central sulcus and that the thalamo-cortical volley may show significant temporal dispersion. Spread to cortex behind the intraparietal sulcus may occur through a cortico-cortical relay.

The inflexion of the surface-positive wave has been used in this study as the index of the arrival of the afferent volley at the cortical surface. It was initially ascribed to the action potential of impulses propagating up to afferent terminals in the cerebral cortex (Forbes and Morison, 1939; Adrian, 1941). Eccles (1951), however, claims that the surface-positive wave should be ascribed to synaptic excitatory action of afferent impulses on cortical neurons. On this view it should be possible to detect by intracortical recording a brief spike (attributable to the afferent volley and of maximum amplitude in cortical lamina IV) prior to the onset of the surface-positive wave. This spike has been seen only in the visual cortex (Bishop and Clare, 1952), where the onset of the slow wave has been partly correlated with the third spike of the afferent volley and where lamination studies suggest that it may be the response of pyramidal cells at the level of the afferent endarborizations.

The position in the somato-sensory cortex is by no means as clear. Amassian (1953) with microelectrode intracortical recording has concluded that as some cortical cells fire during the time of the surface-positive wave, it suggests, but does not rigorously prove, that some aspect of the cortical cell potential contributes to the primary response. On the other hand Arduini and Terzuolo (1951) consider that in both specific and diffuse thalamic projection systems the surface-positive wave is due to activity in afferent fibres failing to excite trans-synaptically the cortical neurons. Thus, while there is still considerable obscurity about the

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relative significance of the arrival of the afferent volley in the axonal endarborizations, and the ensuing post-synaptic excitation of cortical cells in the production of the surface-positive wave, there appears to be no basic objection to the use of the inflexion of this wave as an index of the arrival of the afferent volley at the cortex.

All evoked potentials have been recorded in this study with monopolar leads. With the changing contours of the sensory cortex in the monkey it was decided that rapid mapping with any form of bipolar electrodes would involve considerable difficulties and risk of cortical damage. Monopolar recording of the surface-positive wave is presumably in a volume conductor where tissues adjacent to the surface behave as "sources" to more deeply situated "sinks" with the active electrode responsive to activity arising a short distance away. The superficial surface-negative response to direct cortical stimulation can be recorded with monopolar leads (Burns, 1951) a few millimetres farther from the stimulus than with bipolar recording (Adrian, 1936). However, our findings do not suggest that the peripheral responses are to be accounted for by the conduction of bioelectric effects from remote foci of activity, since the largest responses were always asymmetrically situated within the responsive field and frequently lay within a short distance of a sharply defined boundary. Moreover, the latency gradients about the point of shortest latency were in every case spatially asymmetric.

The outstanding feature of the representation of body parts within each of the three major cortical "fields" is undoubtedly the great degree of spatial overlap on the cortical surface, such that the total responsive area remains essentially the same from separate stimulation of different digits or widely separated regions of the face. Each limb "field" responds to stimulation of the homolateral limb over almost as large an area as for contralateral stimulation. In view of this spatial overlap, it seeems that conscious localization must depend on the assessment of afferent data in a cortical area of appreciable size. The spatial dispersion of impulses in what may be regarded as limb and face "fields" or "pools" does not provide a satisfactory explanation of cortical localization.

On the other hand, our results in the monkey, and those from similar studies in the prehensile forepaw of the marsupial phalanger (Adey, Carter and Porter, 1953), suggest that there are constant differences in the pattern of temporal dispersion of impulses within this responsive field. Thus the zones of shortest latency for the first, third and fifth digits of the hand lie at successively higher levels in the cortex adjoining the central sulcus. The short latency zone for the thumb adjoins but does not overlap the corresponding one for the ophthalmic

division of the trigeminal nerve, despite appreciable spatial overlap in the representation of thumb and face in this cortical region.

When determined from these short latency zones, the relative cortical dispositions of the first, third and fifth digits of the hand and of areas supplied by the three divisions of the trigeminal nerve agree well with those in man determined subjectively by cortical stimulation (Penfield and Rasmussen, 1950) and in the monkey from tactile stimulation (Woolsey, Marshall and Bard, 1942). The figures of the latter investigators show plainly that with an experimental method the converse of our own, in recording from a fixed cortical point the latency of the evoked response varies greatly with changing sites of peripheral stimulation. Bartley (1936) observed that in the visual cortex each retinal point has a focal cortical point where impulses arrive first with later and smaller potentials in surrounding areas, and suggested that maximal activity at any cortical point might result from convergence of impulses on common synapses under appropriate temporal conditions.

Ipsilateral leg responses similar to those described here have been reported in the monkey from stimulation of the central end of the cut sciatic nerve (Malis, Pribram and Kruger, 1953) and in somatic areas I and II of the cat from stimulation of limb and neck musculature (Mickle and Ades, 1952). These responses have also been noted in somatic area I of the rabbit and marsupial phalanger, and under carefully controlled conditions have been shown not to arise from either mechanical transfer or crossed spinal reflex transmission to the contralateral limb (Adey and Kerr, 1953; Adey, Carter and Porter, 1953).

In the monkey the ipsilateral arm and leg responses occur with the most constant waveform near the central sulcus in an area appreciably smaller than the contralateral responsive field, but concentric with it. The latency of the ipsilateral responses remains essentially constant across the area and, as in the rabbit and marsupial phalanger (Adey, Carter and Porter, 1953), is longer than the latency of contralateral responses. They may reach the cortex in "secondary" projection systems as described by Forbes and Morison (1939) and Dell and Olson (1951), since under the nembutal anaesthesia used in our experiments they fail to follow a stimulus rate greater than one every two seconds. They differ from the ipsilateral responses of Forbes and Morison in being confined within the cortical area of the corresponding contralateral representation and have a latency considerably less than 30–60 msec. for the secondary responses of Forbes and Morison. Amassian (1952) has reported bilateral limb responses with a long latency in the cat in association cortex adjacent to the main sensory strip and involving a pathway through the pontine tegmental and medial thalamic nuclei.

It is possible that the ipsilateral responses may be concerned in a form of deep pain perception, since in man after hemispherectomy, despite the loss of all contralateral cutaneous sensation, a form of deep pain sensibility persists in the opposite limbs (Dandy, 1933). It is conceivable that, as originally suggested by Walker (1942), a temporally uniform volley such as we have described reaching the ipsilateral sensory cortex through the remaining thalamus may have been interpreted in consciousness as a form of deep pain in Dandy's cases. Dusser de Barenne (1916, 1924, 1931, 1937) noted bilateral representation of the superficial sensibilities in both thalamus and cortex from strychninization studies in the monkey.

Thus the weight of evidence suggests that perception may rest on the examination of patterns and sequences of afferent impulses rather than merely on spatial dispersion of impulses at the cortical surface. The ability to identify and localize simultaneous asymmetric tactile stimuli develops gradually during the first decade of life (Fink and Bender, 1953). The errors in this asymmetric stimulation, involving extinction, displacement and reference of the stimulus to a symmetrical point on the opposite side of the body, all suggest that sensory discrimination is a learned process involving the interpretation of patterns and sequences of stimuli.

The present study and similar investigations in the marsupial phalanger and rabbit (Adey, Carter and Porter, 1953) support the view that temporal integration may be of basic importance in the process of perception. As Klüver (1953) has remarked, each stimulus or group of stimuli does not possess a unique significance represented by particular responses, but that stimuli are given different significance if they occur in combination with or are evaluated in the light of a great number of other stimuli. Microelectrode recording of single cortical cellular responses to peripheral stimulation gives little information as yet about possible mechanisms for evaluation of the afferent data reaching the cortex (Amassian, 1953).

Summary

(1) The cerebral representation of certain forms of deep somatic sensibility have been mapped in five specimens of the rhesus monkey (*Macacus rhesus*).

(2) Electronic stimulation of deep structures indicates that there is the same basic arrangement of body regions on the cortical surface as previously described for tactile sensibility. The face, arm and leg representations each form a major "field" or "pool."

(3) The extent of the responsive cortex appears significantly larger than that previously described for tactile sensation. Much of the leg area

lies in the precentral region, and appreciable though smaller portions of the arm and face areas have been constantly noted in precentral cortex. Responses in arm and face areas extend posteriorly into cortex behind the intraparietal sulcus.

(4) In stimulation of the hand, the total responsive area remains essentially constant in size and disposition from stimulation of the first, third and fifth digits and the distal forearm. Similarly in the face area, there is a high degree of spatial overlap from peripheral stimulation of widely separated points. However, the cortical point within this area yielding the most rapid responses is constant in position for each site of peripheral stimulation. These short latency zones lie in the vicinity of the central sulcus.

(5) It is suggested that perception and localization may occur in each of the major cortical sensory "fields" in terms of the disposition of the point of shortest latency within an activated "field" of essentially constant site and dimensions. When mapped from these short latency zones, the relative dispositions of the digits of the hand and the regions of the face agree well with those determined subjectively in man by cortical stimulation.

(6) Ipsilateral responses have been noted in both arm and leg areas. The responsive area in each case is smaller than that from contralateral stimulation, but concentric with it. The ipsilateral responses show a relatively constant latency in the exposed cortex without the central shortening noted with contralateral stimulation. The possible relationship of these ipsilateral responses to the perception of certain forms of deep pain is discussed.

Acknowledgments

It is a pleasure to acknowledge the continued help and encouragement of Professor A. A. Abbie in all aspects of this study. Mr. B. Hill and Mr. A. Buxton have rendered valuable technical aid and Miss G. Walsh has assisted in the preparation of the illustrations.

Abbreviations Used in Text Figures

fiss. lat., lateral fissure.
s. arc., arcuate sulcus.
s. cent., central sulcus.
s. intrap., intraparietal sulcus.
s. lunat., lunate sulcus.
s. parall., parallel sulcus.
s. postcent. sup., superior postcentral sulcus.
s. precent. sup., superior precentral sulcus.
s. rect., sulcus rectus.
Vi. ophthalmic trigeminal representation.
Vii. maxillary trigeminal representation.
Viii. mandibular trigeminal representation.

PLATE VII

Cathode-ray oscillograph recordings of evoked cortical responses. Arrows in figs. 2 and 3 indicate stimulus artefact. Time-marker in all records, 50 cycles per second. Downward deflection indicates positivity in all tracings.

FIG. 1.—Reponses in 2 mm. steps from stimulation in contralateral maxillary trigeminal area. All responses recorded in postcentral cortex.

FIG. 2.—Responses in 2 mm. steps from stimulation of ipsilateral arm. Records 2A—2D obtained precentrally, records 2E—2H from postcentral cortex.

FIG. 3.—Responses in 2 mm. steps from stimulation of ipsilateral leg. Tracing 3C recorded postcentrally, all other responses mapped precentrally.

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PLATE VII

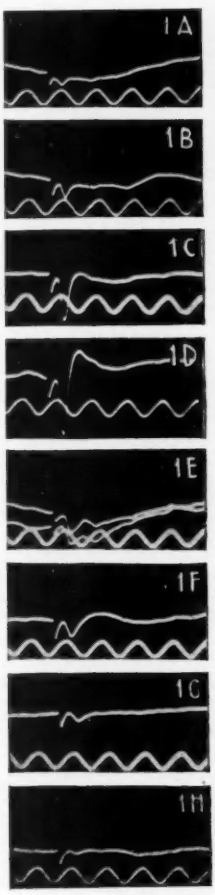

FIG. 1.

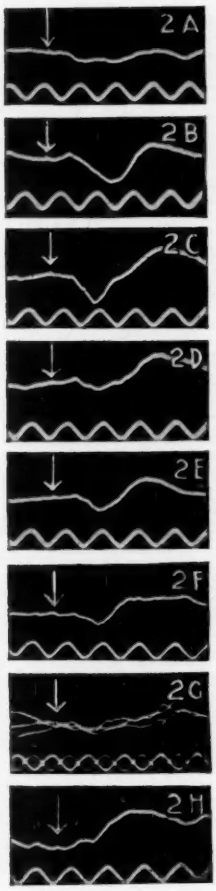

FIG. 2.

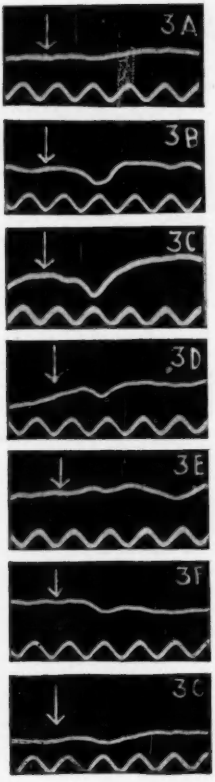

FIG. 3.

To illustrate article by W. R. Adey, R. Porter and I. D. Carter.